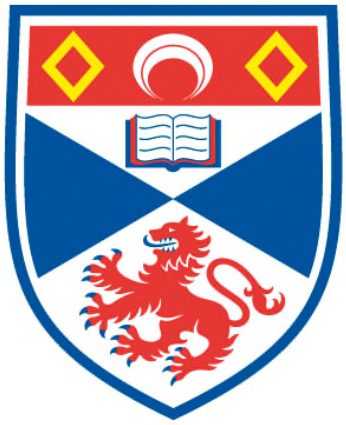
THE PREPARATION AND TESTING OF NOVEL BIODEGRADABLE SURFACTANTS USING POLY(LACTIC ACID) AS THE BACKBONE, BY A ONE-STEP RING OPENING POLYMERISATION REACTION

Gavin T.H. Hill

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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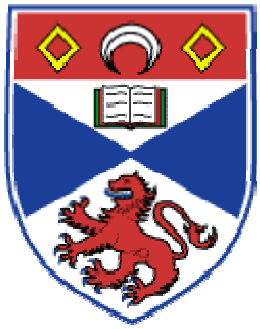

University
of
St Andrews

Thesis Submitted
for Examination for Degree of Doctor of Philosophy

Gavin T H Hill

DECLARATION

I, **Gavin Thomas Hamilton Hill**, hereby certify that this thesis, which is approximately **50,000** words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in **September, 2004** and as a candidate for the degree of Doctor of Philosophy in **August, 2005**; the higher study for which this is a record was carried out in the University of St Andrews between 2004 and 2008.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Contents: i

List of Abbreviated Terms

12-HSA	12-hydroxystearic acid
BHB	2,2-bishydroxymethylbutyrate
ChCl or Cho	Choline Chloride
CMC	Critical Micelle Concentration
ΔCp	Heat Capacity
DCM	Dichloromethane
DDE	Dichlorodiphenyldichloroethylene
D,L-lactide	3,6-Dimethyl-1,4-Dioxane-2,5-Dione
DLS	Dynamic Light Scattering
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DSC	Differential Scanning Calorimetry
ESMS	Electrospray Mass Spectroscopy
Eut	Eutectic mixture
FDA	Food and Drug Administration (US)
GHB	γ-hydroxybutyrate
GPC	Gel Permeation Chromatography
HBuA	2-hydroxybutyrate
HHxA	2-hydroxyhexanoate
HiVA	2-hydroxyisovalerate
HOctA	2-hydroxyoctanoate
IR	Infra Red Spectroscopy
L : I	lactide to initiator ratio
L-lactide	(3S)-cis-3,6-Dimethyl-1,4-Dioxane-2,5-Dione
MALDI-TOF	Matrix Assisted Laser Desorption Ionisation - Time of Flight
Man or Mandela	Mandelate
MeOPEG	Methoxypoly(ethylene glycol) or poly(ethylene glycol) monomethyl ether
M_n	Number Average Molecular Weight

M_p	Peak Average Molecular Weight
M_w	Weight Average Molecular Weight
Mwt	Molecular Weight
NMR	Nuclear Magnetic Resonance
O/W	Oil in Water Emulsion
PDI	Polydispersity Index
PLA; PLLA	Poly(lactic acid); Poly(L-lactic acid)
ROP	Ring Opening Polymerisation
PCB	Polychlorinated biphenyls
PEG	Polyethylene glycol
PEO	polyethylene oxide
RT	Room Temperature, 20-23 ^oC
$Sn(oct)_2$	Tin (II) bis-ethylhexanoate, stannous octanoate
ST	Surface Tension
T_c	Post Crystalisation Temperature
T_g	Glass Transition Temperature
THF	Tetrahydrofuran
T_m	Melting Temperature
TGA	Thermal Gravimetric Analysis
UV	Ultra-violet spectrometer
W/O	Water in Oil Emulsion

List of Standard and Non-standard Units

Amu	atomic mass units
LA units	lactic acid repeat units (72 amu)
mNm^{-1}	units of surface tension
nm	nanometres
ppm	parts per million
$J\ (g\ K)^{-1}$	units of heat capacity

Abstract

A review of the chemistry of poly(lactic acid) was carried out with a focus on techniques and applications of PLA polymer and copolymers with reference to some of the work that has been accomplished over the last 20 years or so. A review of the characterisation techniques used to analyse PLA polymers and copolymers was also carried out giving reference to the equipment and methods used herein.

An investigation into the potential of PLA as the hydrophilic portion of a polymeric surfactant was carried out. To develop PLA based surfactants, the ring opening polymerisation of lactide was carried out in a melt in the presence of a long chain alcohol (C_7 to C_{20}) or diol (C_4 & C_6) to produce AB or ABA type polymers that follow the traditional surfactant template. Stannous octanoate and 4-dimethylaminopyridine were typically used as catalysts due to their high activity and relative cheapness. PLA only shows good hydrophilicity with up to 12 lactic acid units in the chain. Above this the electrostatic interactions between polymer chains reduced water solubility. It was also noted that D,L-lactide produced more water soluble polymers (syndiotactic) than the enantiomerically pure L-lactide (isotactic polymer chains).

An investigation of the hydrophobic properties of PLA was carried out to evaluate their usefulness for other biodegradable surfactant applications. To this end an investigation of sugars as the hydrophilic portion of the molecule was carried out. Due to problems with solubilising sugars, they were deemed unsuitable for use as initiators within the scope of this research.

Choline chloride was then investigated as a potential hydrophilic initiator and indeed has produced some of the most water soluble of PLA polymers. Choline chloride presented several challenges as an initiator, its high melting point resulted in polar solvents such as *t*-butanol being employed. Alternatively, more success was achieved by preparation of a choline chloride eutectic mixture prior to the polymerisation. It was discovered that a choline chloride/urea eutectic mixture was capable of self initiation, thus required no further addition of catalyst, this result shows a potential step forward in PLA green chemistry.

A final investigation into producing surface-active PLA in a one-pot process that required only a hydroxycarboxylate initiator was carried out. The production of PLA sodium or potassium salts was carried out in a melt polymerisation and the results show some promise. Initiators that have been employed include a range of α, β and γ-hydroxycarboxylic acids. These work through tautomerisation to the alkoxide, which then initiates a living type polymerisation of lactide to produce surface-active polymers.

As well as the synthesis of these polymers some analysis of the physical and aqueous properties of these materials was carried out. PLA sodium salts were shown to have reasonable surfactant ability (~45 mNm^{-1}) and low CMC values of around $5x10^{-9}$ mol cm^{-3}. They were also shown to have some properties as emulsifiers, and in some cases showed non-Newtonian fluid behaviour such as shear-thinning (thixotropy) and shear-thickening (dilatant). The thermal characteristics of the polymers such as T_g and stability were assessed as well as their ability to retain water.

Chapter 1:
An Introduction to Lactide Polymerisation

1.0 Aim

The aim of this chapter is to illustrate the importance of lactide polymerisation for sustainable development of biodegradable and biorenewable polymers. To look at how the subject has evolved since the discovery of poly(lactic acid) and Ring Opening Polymerisation (ROP) by researching:

1) The global economic and ecological benefits of poly(lactic acid) over other polymers
2) To analyse the different methods used for lactide polymerisation, in terms of the catalysts, solvents and reaction methodology.
3) To look at polymer and copolymer structure and how structure can be tailored to produce the desired physical properties.
4) To introduce how this work has led to the evolution of the work to be described within the chapters to follow.

1.1 Poly(lactic acid) today

Poly(lactic acid) (PLA) is a biodegradable polymer produced from a biorenewable feedstock. It is commercially produced in two key reaction processes but the starting point for both processes is lactic acid. Lactic acid (2-hydroxypropanoic acid) is a compound produced by the fermentation of carbohydrates such as glucose and sucrose (the main natural feedstock being corn) in a variety of natural processes i.e. in the muscles during exercise as carbohydrates are combusted and by some types of bacteria (lactobacilli). PLA can be prepared either by direct condensation polymerisation of lactic acid or by ring opening polymerisation of lactic anhydride (lactide). Lactide is prepared by slow distillation or by vacuum distillation of lactic acid.

There has been considerable interest in lactide polymerisation over lactic acid polymerisation over the last 20 years, as it has several benefits over the direct condensation route:

1) It is not an equilibrium reaction
2) No water is produced which can lead to hydrolysis
3) Faster and cleaner reactions can be carried out
4) It can be used to produce higher molecular weight products

Poly(lactic acid) polymers have been used for many years in medicine as dissolving sutures and as biodegradable and biocompatible materials for use as control release measures for drug delivery [1,2]. Over the last decade, due to the commercial availability of lactic acid and lactide it has found more widespread use in plastics.
PLA is a thermoplastic and has similar physical properties to polystyrene, which makes it ideally suited for: injection moulding, sheet extrusion, blow moulding, thermoforming, film forming and fibre spinning. PLA is so completely versatile that it can be used to reproduce the properties of almost any polymer material currently available.

PLA has obvious benefits and some possible problems. It's obvious benefits come in the form of relief from the demands of oil derived polymers as it can be produced from entirely natural resources by fermentation of sugars from corn and potato starch; sucrose from cane or sugar beet; and lactose from cheese whey. In Western Europe we are fortunate to have a surplus of dairy produce and cereals due to the European Union's common agricultural policy and this may offer a commercially and environmentally friendly way to consume this surplus. On one hand this has obvious benefits to the agricultural industry since it will have to supply huge amounts of biomass to be converted to lactide. The global trend for biorenewable polymers and biodiesel has led to one major concern, which is that the price of corn has risen 50% in a year. This is a serious problem because corn is a staple of the diets of many people especially in poorer countries.

1.1.1 Current Commercial Processes

The first commercial processes for the production of poly(lactic acid) were introduced in the 1990's. There have been two important developments; the first was Mitsui Toatsu Chemicals patent of an azeotropic distillation process that used a high-boiling solvent (toluene or xylene) to remove water formed during the lactic acid polymerisation. In order to obtain higher mwt products these polymer chains are then directly esterified (chain extension polymerisation). The second was the formation of Cargill Dow in 1997 that are now one of the world's largest producers of biodegradable polymers from biomass [3].

Cargill Dow was a marriage of two companies with the focus towards PLA and lactide production. Their aim was to reduce the production costs and to produce PLA in huge quantities. The process they have developed is a low cost continuous process for production of lactic acid based products [4].
Their reactors synthesise both lactide and PLA in a melt reactor, (see Figure 1.1).

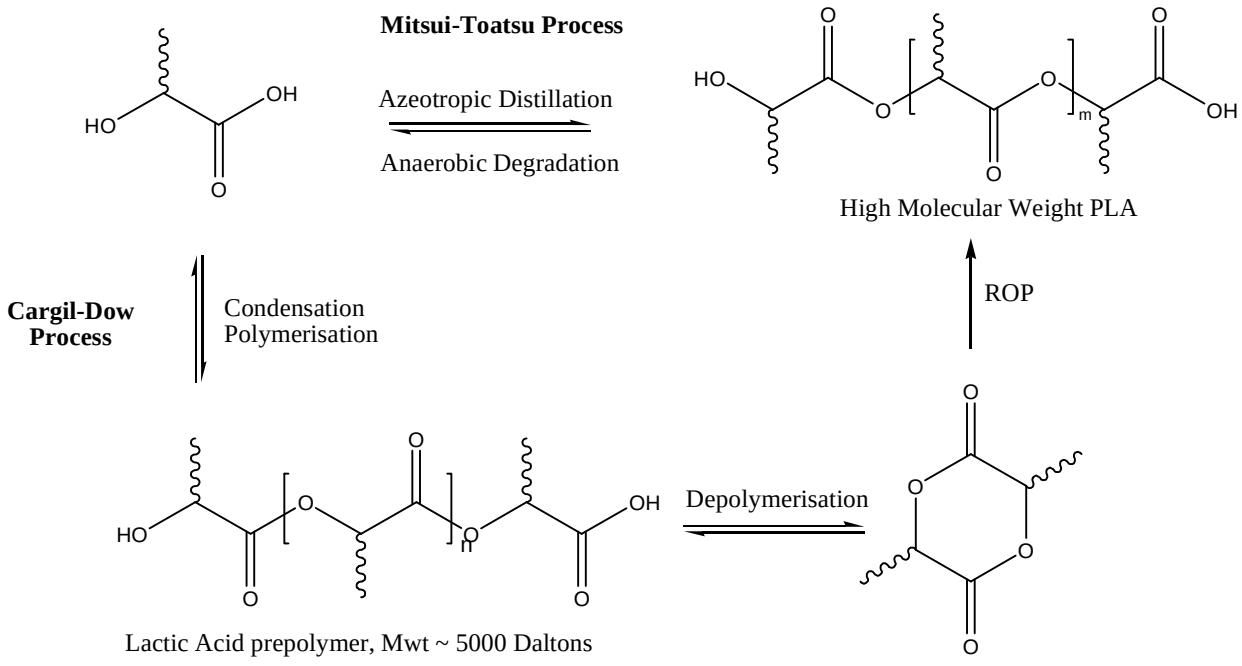


Figure 1.1.1: Cargill Dow Route to High Molecular Weight PLA.

The first phase of the reaction is to produce a low molecular weight PLA pre-polymer, via continuous condensation polymerisation. The pre-polymer is then

converted to *rac*-lactide (D,L) and purified. The next step is the ring opening polymerisation of lactide using a tin alkoxide/carboxylate catalyst (usually tin (II) bis-ethylhexanoate, or tin (II) butoxide) to produce the high molecular weight, polymers. It is an environmentally friendly synthesis, starting with biorenewable feedstocks and no organic solvents are required. Remarkably it also produces two valuable products in lactide and PLA and has developed methods of reducing waste of the biomass left over from the polymerisation by use in ethanol production or for fuel for plants.

1.1.2 Poly(lactic acid) Degradation

PLA undergoes natural aerobic and anaerobic degradation processes in which it is decomposed to environmentally benign lactic acid, carbon dioxide and humus. In the initial stages of decomposition the hydrolysis of high molecular weight PLA to lower molecular weight products is very important. The rate of this reaction can be increased by the presence of acids or bases (or even by trace catalyst). Degradation is also sensitive to temperature and moisture levels [2,3]. At a molecular weight of less than 40 000 Daltons microbial degradation can occur. Microorganisms found in soil and in aquatic environments can convert these lower molecular weight polymers to carbon dioxide, water and humus (as seen in Figure 1.1.2).

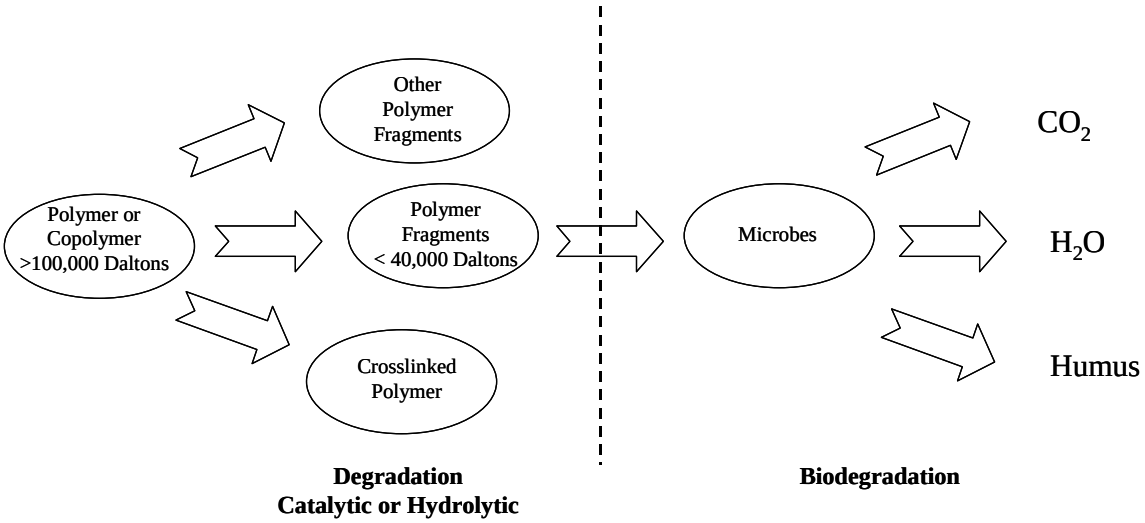


Figure 1.1.2 shows a general degradation cycle of polymers or copolymers.

One of the problems with degradation/biodegradation is within its definition. For a material to be classed as biodegradable a polymer or copolymer must show a

loss in mass of 60% or 90% respectively in a time frame of <180 days. However, even within the scientific literature there are some questionable claims that, although correct by definition, are misleading and, if taken seriously, could dramatically increase another environmental problem "white pollution". One such example is a paper by Gokhale *et al.* [5] where they describe grafting sugars onto polystyrene and poly(styrene-co-maleic anhydride) enhancing their biodegradability. However, they only recorded a loss in weight of 2-12 % over 25 days, which is not enough to be considered biodegradable. What this merely suggests instead is that the bacteria they used *Serratia marsescens, Pseudomonas sp* and *Bacillus sp*, removed all trace of the sugars but left the polymers largely intact.

"White pollution" is a massive worldwide problem. In the UK roadsides are littered with polymer waste from cars, litter and plastic bags are caught in trees, shrubs and pylons. This can be a greater problem when polymers enter into aquatic systems, rivers and streams and this has been a massive problem in China. There is a second problem with plastic degradation and that is micro/nano-particulated plastics that are small and hugely mobile in both air and aqueous environments. The incomplete degradation and physical wearing of plastics in the environment produce these. As yet the effects on the human body are largely unknown but they may act as a method by which other toxins could enter the human body in particular PCB's, DDE and nonylphenols, can stick to hydrophobic plastic particulates in marine environments [6].

An interesting study on polymer degradation actually showed plants thriving in soil containing poly(lactic acid) and poly(3-hydroxybutyrate) blends [7]. This study illustrates that biodegradable PLA is not environmentally benign, but may have some environmental benefits making it a useful polymer in the agricultural industry.

1.2 Ring Opening Polymerisation

The main focus of research into *ring opening polymerisation* of lactide over the last 20 years has been on: the different catalytic process, the formation of copolymers and the polymer characterisation. In general for PLA production there are two important factors, the catalyst and the initiator. The catalyst is the most important factor, choosing the right catalyst can negate the need for a further nucleophilic initiator. For high molecular weight PLA the most common initiators are methanol, ethanol and isopropanol, although phenyl alcohols have also been favoured and are used for studying ligand mediated processes.

Ring opening polymerisations (ROP) are important reactions in polymer chemistry and can be used to produce a wide variety of polymers such as polyalkenes (Ring opening metathesis polymerisation, ROMP), polyamides (from lactams), polyamines (Aziridines), polyethers (trioxane, epoxides) and polyesters (lactones).
The largest commercial process in ring opening polymerisation is the polymerisation of epoxides, ethylene and propylene oxide. Epoxide reactions are favourable due to the strain of the three membered ring and polymers of ethylene oxide and propylene oxide have been commercially used for many years [8]. However, due to the decline in oil reserves an ever-greater demand for polymers from bio-renewable feedstocks has led to the development of ring opening polymerisations of a wide range of cyclic esters and other strained molecules such as ε–caprolactones [9] and lactide.

Ring opening polymerisation (ROP) of cyclic esters has been known for over 100 years. ROP of glycolide was first noted by Bischoff and Walden (1893) [10], they discovered that glycolide, under the influence of heat or catalytic amounts of zinc chloride, formed a polymeric solid at 220 ^{o}C, but, on being distilled under vacuum this polymer was reconverted to the monomer.

The ring opening polymerisation of lactide was not carried out until much later, when the pioneering work by Carothers, Dorough and Van Natta was published in 1932 [11]. They found that lactide formed a resinous mass (Mwt 3000) at temperatures exceeding 250 ^{o}C or at a lower temperature. It was found that addition

of a potassium carbonate catalyst (140 – 150 ^{o}C) would produce a similar effect at lower temperature. Their work on base catalysed polymerisation has formed a fundamental basis of lactide polymerisation. In their reactions it is likely that at the high temperatures, the presence of water impurities caused hydrolysis of the lactide, forming a lactic acid dimer (lactoyl lactate). The alcohol produced can then attack other lactide rings at the carbonyl, resulting in ring opening of a second lactide ring and thus polymerisation occurs.

The ROP of lactide using a hydroxide base in the presence of a suitable nucleophile, such as an alcohol, illustrates best the simplest mechanism for the ROP of lactide, shown in Figure 1.2.

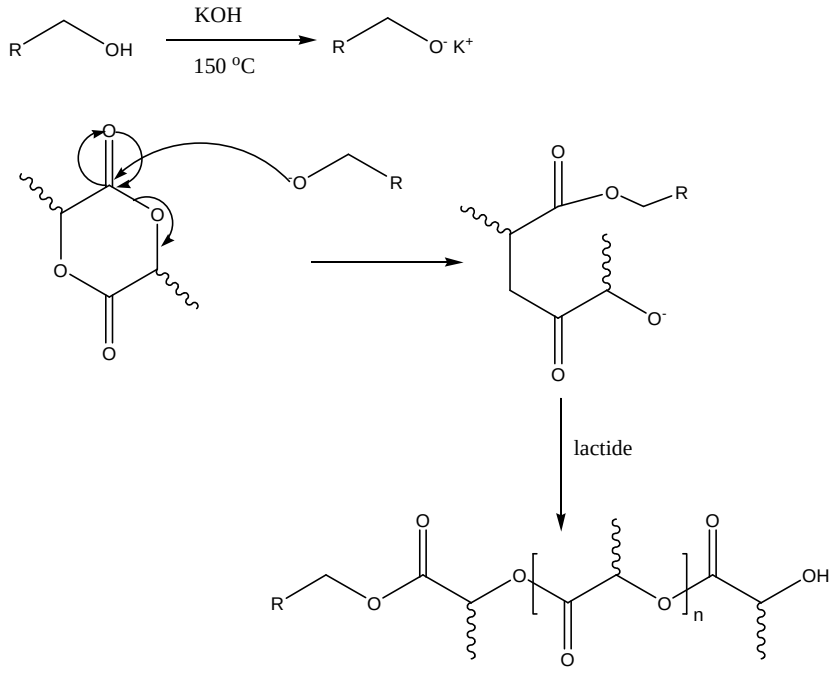


Figure 1.2: Base catalysed ROP of Lactide.

It involves the removal of the acidic proton from the alcohol and subsequent attack of the alkoxide anion at the carbonyl that causes the ring to open and the production of a new alkoxide species. This reaction can also occur at high temperatures, simply by nucleophilic attack by the alcohol on the carbonyl.

What this work would lead to was the concept that any transesterification catalyst would be a viable catalyst for lactide polymerisation. Strong bases are known

to act as potent transesterification catalysts as they promote nucleophilic attack from chain ends. The most commonly used transesterification catalysts for polyester production are titanium and tin alkoxides.

1.2.1 Organometallic Catalysed ROP

The development of organometallic catalysts for the living polymerisation of lactide has become an important and competitive area of chemistry. The demand for catalysts to be more environmentally friendly and have lower in-vitro toxicity has been part of the drive. Lactide polymerisation has also become a good model reaction for many groups to test out their new catalyst systems where they have studied different metals and ligand systems and the elucidation of new different mechanistic pathways. The main process of ligand design is in producing enantioselective ligands to produce L-PLA or D-PLA selectively from D,L-lactide, as the racemate is much cheaper starting material than either the D or L-lactide.

Some work has been carried out on complexes of the alkali and alkaline earth metals, but with the exception of magnesium [12] and calcium [13] have been shown to be poor catalysts.

Transition and main group metal catalysts especially those that can undergo covalent type bonding, have proven to be among the best catalysts for lactide polymerisation. There has been much success with catalyst complexes of yttrium, zinc, iron, aluminium and tin as well as many of the Lanthanides. There are also several other heavy metals that have shown activity for ROP of lactide including complexes of lead, bismuth and antimony, which are generally unsuitable due to toxicity.

The toxicity and the expense of the catalyst has become the most important factor industrially, as the catalyst may often be difficult to remove or recycle. It is important that the catalyst has good solubility in the reactants, but the catalysts solubility in the products could be more problematic as this will govern how easy the catalyst is to remove.

Different groups have approached these metal catalysts in different ways. In some cases they are interested specifically in different ligand and multi-nuclear systems. The main aim however, has been to produce high molecular weight poly(lactic acid) with controlled stereochemistry and predictable molecular weights. Much of the work has been focussed specifically on non-toxic metals such as zinc, magnesium and calcium as they are present in the body (found in enzymes, bones etc) and trace amounts of catalyst in the products will not cause any dangerous side effects nor be hazardous to the environment upon degradation.

Whereas, complexes of yttrium, tin (IV) and aluminium (III) have known toxicities in the body, aluminium for instance has been linked with Alzheimer's disease. Commercially, stannous octanoate is the most commonly used catalyst as it is cheap and produces polymers of predictable molecular weights. These metal alkoxide catalysts are of interest for tailor making polymers or co-polymers of various size and structure.

Living polymerisation initiated by metal alkoxides has several advantages in that the catalyst and initiator are one and the same. For high molecular weight polymers, very little catalyst is required which, economically speaking, is good. However, in order for these more complex metal alkoxides to find widespread use, they will need to be cheap since the catalyst cannot be easily removed or recycled.

1.2.2 Tin (II) and Tin (IV) Catalysed Processes

Among the earliest and most widely used catalysts in the ROP of cyclic esters are the tin carboxylates and alkoxides. Tin (II) bis-ethylhexanoate (stannous octanoate; $Sn(oct)_2$) [1,4,14,15,16 & 17] is the most widely used catalyst, and surprisingly for a tin compound has very low toxicity and has been FDA approved. It is used since it has high catalytic activity and produces high molecular weight polymers with low racemisation. Another major benefit is that it is very soluble in the lactide and polylactide melt. The originally proposed mechanistic pathway using stannous octanoate is shown in Figure 1.2.2a [1], and the currently accepted mechanism is shown in Figure 1.2.2b [14].

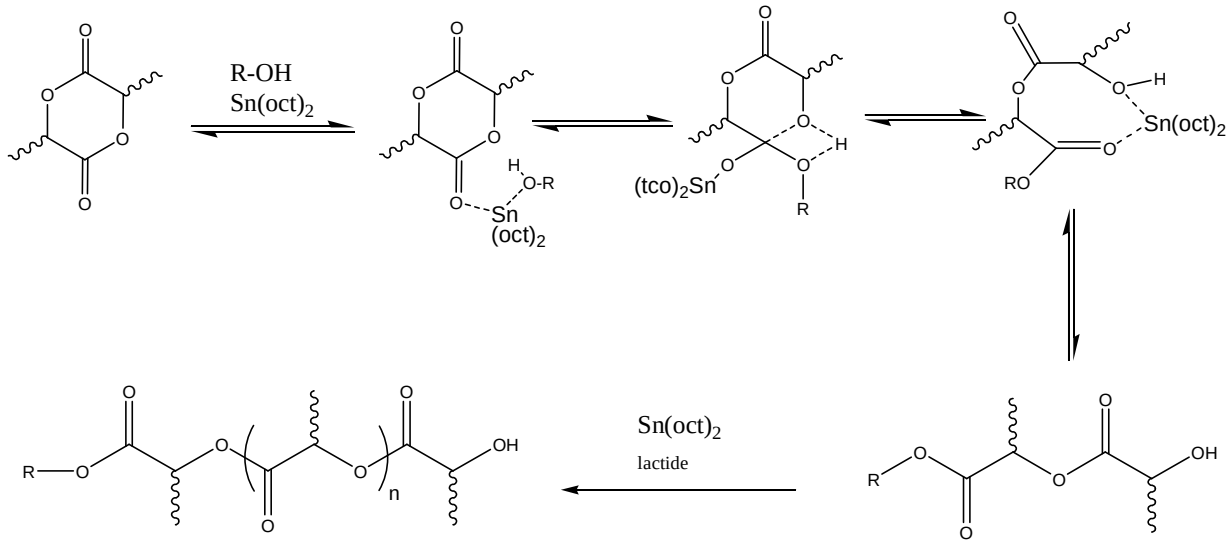


Figure 1.2.2a. The Originally Proposed stannous octanoate catalysed mechanism.

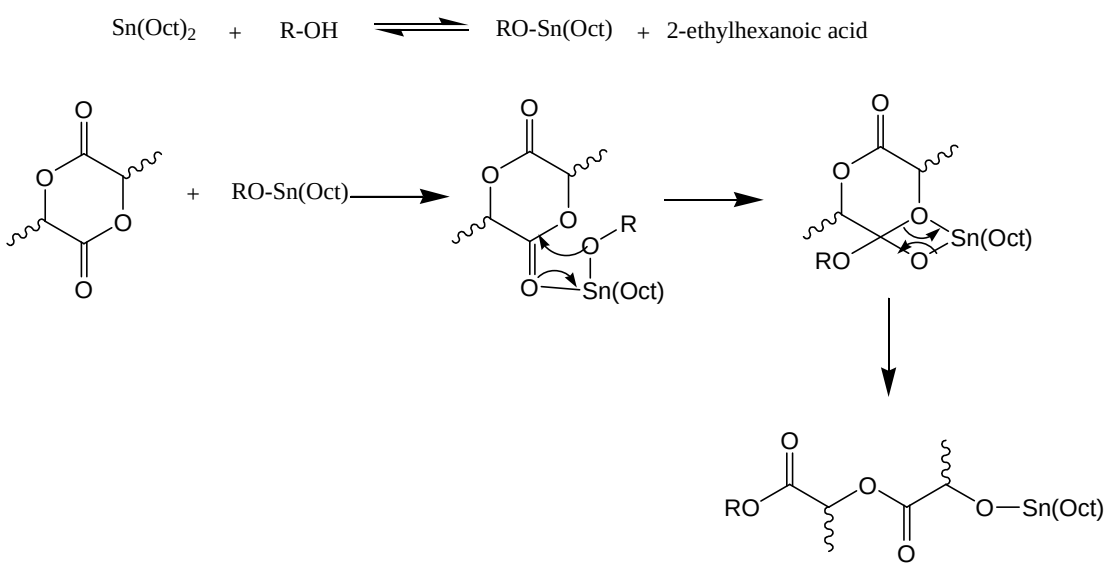


Figure 1.2.2b. The now accepted mechanism, where the active catalyst is a newly formed stannous alkoxide.

From the initially proposed mechanism it can be seen that the tin complex promotes the addition of the alcohol to the lactide by mediating the reaction. The tin catalyst performs several key tasks, it associates to the alcohol and to the lactide ring through the carbonyl oxygen, and the alcohol can then react at the carbonyl. As a Lewis acid the tin reduces the electron density from the CO bond and makes the carbon more electrophilic and promotes deprotonation of the alcohol to give the more nucleophilic alkoxide. The reaction goes through an 8 membered ring type transition state, with the formation of an ester end group, the linear product (alcohol terminus)

can then react with another lactide ring, mediated further by the presence of $Sn(oct)_2$. The benefit of this reaction in terms of the preparation of short chain polymers is that only a catalytic amount is required, around 5 mol % in relation to the alcohol initiator.

In the now accepted mechanism the ROP of lactide is preceded by the formation of a stannous alkoxide (with loss of one or both of 2-ethylhexanoate ligands) that undergoes the co-ordination insertion mechanism known for other metal alkoxide species (Section 1.2.4).

As well as tin (II) compounds some tin (IV) complexes have also been tested with some success [18], but the toxicity of most tin (IV) complexes is a major drawback at least in terms of an environmentally friendly reaction and product, as the catalysts are often difficult to remove.

A recent advance in the chemistry of the tin (II) carboxylate catalyst is that it has been used in ROP of lactide in supercritical CO_2 [19,20].

1.2.3 Ferric Alkoxides and Other Iron Species for ROP of Lactide

For the ROP of lactide, many iron compounds have been tried; from ferric oxide to iron lactate. Most have been found to be slow to initiate polymerisation and usually require high temperature, however, more successful in use have been the ferric alkoxides.

Ferric alkoxides are the most widely reported iron catalysts used in the polymerisation of PLA. Iron is attractive as a transition metal catalyst due to it being cheap, abundant and of low toxicity. Due to the presence of iron in the body, any trace amounts of catalyst present in the polymer should have no ill effects, and this makes iron alkoxides particularly useful catalysts for PLAs for biomedical applications. Early work has focussed on iron ethoxide and has led to further investigations into the structure of other ferric alkoxides. This led to the discovery of an oxo-bridged penta-nuclear cluster and a dimeric iron complex, which were isolated and characterised [21]; the crystal structure is shown in Figure 1.2.3. Both seemed to be active for the polymerisation of lactide and these complexes showed higher rates of polymerisation, better control over molecular weight distribution and lower

epimerisation relative to any of the previously reported iron catalysts. The penta-nuclear species catalysed reactions showed the presence of an ethoxy ester end group. Whether longer chain iron alkoxide catalysts could be produced via this method could be interesting.

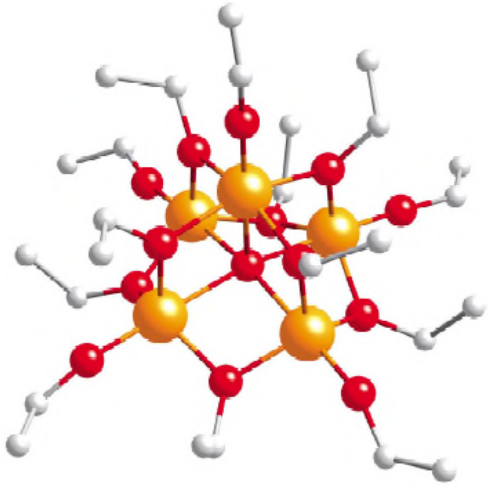


Figure 1.2.3 The crystal structure of the Iron pentanuclear $Fe_5(O)(OEt)_{13}$ complex. Fe is shown in orange; O in Red and C in white.

A recent paper [22] used simple ferric alkoxides ($Fe(OR)_3$) in the ROP of lactide. The ferric alkoxide catalysed reaction proceeds through the same co-ordination insertion mechanism as for previously reported alkoxides (as illustrated in Figure 1.2.4). The ligands of the ferric alkoxides played an important role in the ROP of rac-lactide, the more bulky ligands (isopropoxide and *n*-butoxide) gave lower molecular weight products and a broader molecular weight distribution. Racemisation did not occur in polymerisation of L-lactide, but in polymerisation of *rac*-lactide they noted transesterification occurred, as indicated by the presence of 72 mass units (lactate) separation in MALDI-TOF. If the transesterification process does not occur, lactide is incorporated intact and the mass spectra peaks are separated by 144 amu. Transesterification is a side reaction that occurs in polyester synthesis due to the presence of active chain ends. In the case of ROP of lactide this can occur during or after the ROP process – where active chain ends randomly attack the polymer chain causing cleavage of one chain and extension of the other.

1.2.4 Essential Element Catalysts of Magnesium, Calcium and Zinc

Zinc, magnesium and calcium have attracted some attention as possible PLA catalysts as they are present in the human body and thus have a low toxicity compared to other metals. The ions are often colourless and of low cost. Much of the work on magnesium, zinc and calcium has been on different types of ligands not only for selective catalysis to produce enantiomerically pure PLA, but also to control the lability of the metal ions. One of the problems to be overcome was to inhibit their natural biological function, i.e. to inhibit ligand exchange equilibria and to control the nuclearity. This was achieved by producing complexes that were encapsulated by sterically hindering multidentate N-donors.

An obvious benefit with regards to high molecular weight PLA synthesis is that these reactions are living polymerisations and thus can be carried out without the aid of an alcohol initiator. Zinc [23,24,25,26], and magnesium [24,25,27] and calcium alkoxides [13] act both as catalyst and initiator, a single site catalyst, so in essence providing 1:1 catalyst to initiator ratio, which is ideal since there is no unreacted initiator. The general metal alkoxide reaction is shown in Figure 1.2.4. It is the same as for the accepted $Sn(oct)_2$ mechanism (Figure 1.2.2b).

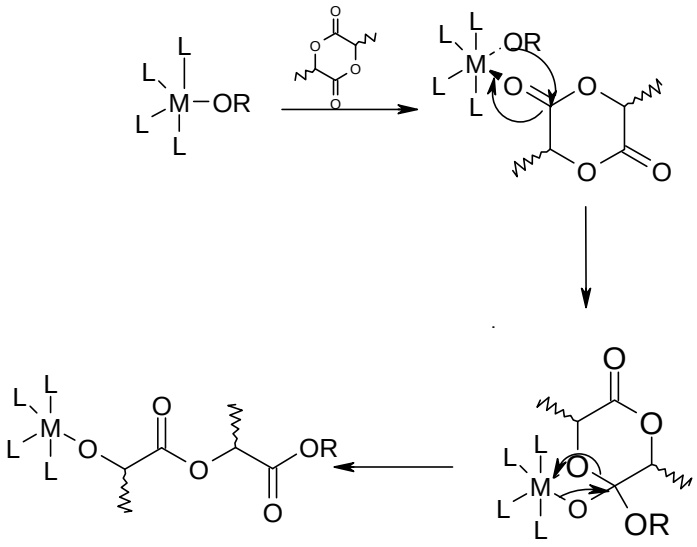


Figure 1.2.4: Living Ring Opening Polymerisation of lactide shows coordination insertion followed by acyl oxygen cleavage.

It has been found the magnesium catalysts work better and under much milder conditions: 22 ^{o}C in DCM as opposed to 110 ^{o}C. These catalysts were also found to

control the stereochemistry and showed some degree of chain end control that was predictable depending on the optical purity of the lactide used. L-lactide produces isotactic, meso-lactide produces syndiotactic and rac-lactide produces heterotactic lactide. The differences will be discussed later, and may only be interpreted by NMR experiments. The properties of the polymers differ depending upon the tacticity (combination of stereo-sequences along a chain). Isotactic PLA is brittle due to being highly crystalline, however altering the tacticity or producing polymers of alternating tacticity the physical properties of the polymer can be tailored to the required needs.

Theoretically of course, these catalysts could be used to produce poly(lactic acid) esters with long chain alcohols. One of the drawbacks being that these catalysts are difficult to synthesise. What is perhaps the most limiting factor is that the catalyst does not dissociate from the chain once attached, the catalyst remains attached to mediate the ROP of the next ring, always producing an active alkoxide species. What may be possible is to produce a pre-catalyst that will form the desired alkoxide in situ.

1.2.5 Aluminium Alkoxides Good Lewis Acid Catalysts

Aluminium alkoxides have also been used with some success as mild ring opening polymerisation reagents (70 ^{o}C in Toluene). In a paper by Feijen *et al.* [28], it was found that the aluminium alkoxide they used polymerised L-lactide significantly faster than D-lactide, which contrasted with results previously obtained with other aluminium catalysts. They also outlined in the paper the use of other aluminium complexes and detailed the development of several PLA microstructures including an isotactic-atactic stereoblock polylactide with a high degree of crystallinity.

In a recent paper by Okuda *et al.* [29] they prepared aluminium complexes supported by [OSSO] type bisphenolato ligands, which were reacted with isopropanol and benzyl alcohol prior to the polymerisation to form the active species for ROP of *rac*-lactide, with the hope that it would produce structurally well defined chains.

1.2.6 Yttrium, the Lanthanides and Other Heavy Metals

Yttrium is another metal that has been extensively studied. Yttrium alkoxides [9] have been employed in much the same way as with aluminium, magnesium and zinc. Yttrium polymerises lactide efficiently and faster than aluminium and early work on an yttrium complex Figure 1.2.6 [21], $Y(OCH_2CH_2NMe_3)_3$ (dinuclear) showed that it could polymerise lactide in a rapid controlled fashion. Interestingly also reported was that the catalytic behaviour was improved upon addition of an exogeneous alcohol or alkoxide into the dinuclear complex.

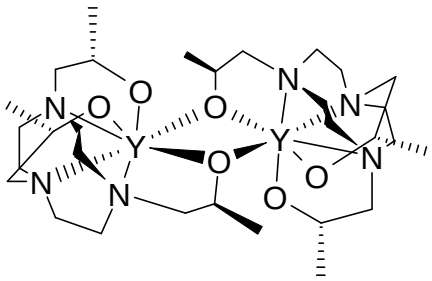


Figure 1.2.6 Dimeric Yttrium Complex found to ROP lactide with an alcohol co-initiator.

They reported that addition of benzyl alcohol did not disrupt the dimeric structure, but that the free alcohol was associated by hydrogen bonding. More interesting though is that this complex was found to result in polymers with low molecular weights and lower molecular weight distributions than produced by the dimer itself. The study also noted that a benzyl ester group was present in the ^1H NMR spectrum, thus confirming initiation by benzyl alcohol.

Yttrium complexes have also been used in the synthesis of a lactic acid and ethylene oxide co-polymer that could be used as a plasticizing agent for poly(lactic acid).

Lanthanide oxo isopropoxide complexes of La, Sm and Yb have also been demonstrated as catalysts for ROP of lactide [21, 30]. The pre-catalyst/catalyst structures however, have not been determined and the mechanistic understanding of these reactions is complicated due to equilibria involving ligand exchange and the changing nuclearity of the species.

A recent study by Kricheldorf [31] has shown the effectiveness of several bismuth (III) compounds, including the drug bismuth (III) subsalicylate, work as a

catalyst in the ROP of lactide. Bismuth (III) subsalicylate is non-toxic and has been extensively used as a drug against gastrointestinal problems for a long time. Bismuth (III) salts have found widespread uses throughout medical applications and its toxicology has been extensively studied. Kricheldorf produced several A-B-A tri-block co-polymers initiated by 1,4-butanediol, of L-lactide, ε-caprolactone and glycolide in the presence of a bismuth catalyst.

It is unlikely, due to the nature of the chemistry involved in the production of poly(lactic acid) alkyl esters that many of these transition metal catalysed reactions will be of much use. However, bismuth (III) subsalicylate and the yttrium dimeric catalyst are interesting and may be useful depending on the interactions with other alcohol initiators. In most cases the catalyst is not regenerated, the catalyst remains attached until the reaction is quenched with the addition of a carboxylic acid and the species formed is no longer the active catalytic species. This leads to problems that make the organometallic catalysed methods unattractive because:

a) They require a large catalyst to monomer ratio to ensure low molecular weight PLA alkyl ester.
b) These catalytic species may be toxic.
c) The catalyst might be difficult and expensive to synthesise.
d) The catalyst activity might be low due to the steric bulk of the alcohol.
e) The catalyst may not be removable from the product.

1.3 Organo-catalysed ROP of Lactide

The production of PLA can also be catalysed using organic Lewis bases and protic acids (i.e. anionically and cationically). These offer reactions that are attractive for a variety of reasons; they do not involve the use of toxic metals, these reagents are cheap and in some cases the reactions can be carried out under relatively mild conditions. These may offer attractive methods of producing PLA that may be well defined and have stereochemical control as well as low toxicity.

1.3.1 4-Dimethylaminopyridine Lactide Polymerisation Catalyst

Among the bases and Lewis bases used for the synthesis of PLA are 4-dimethylaminopyridine (DMAP), 4-pyrrolopyridine (4-PPY) and more recently N-heterocyclic carbenes. The reactions using DMAP have been well studied and the proposed mechanism is given below Figure 1.3.1.

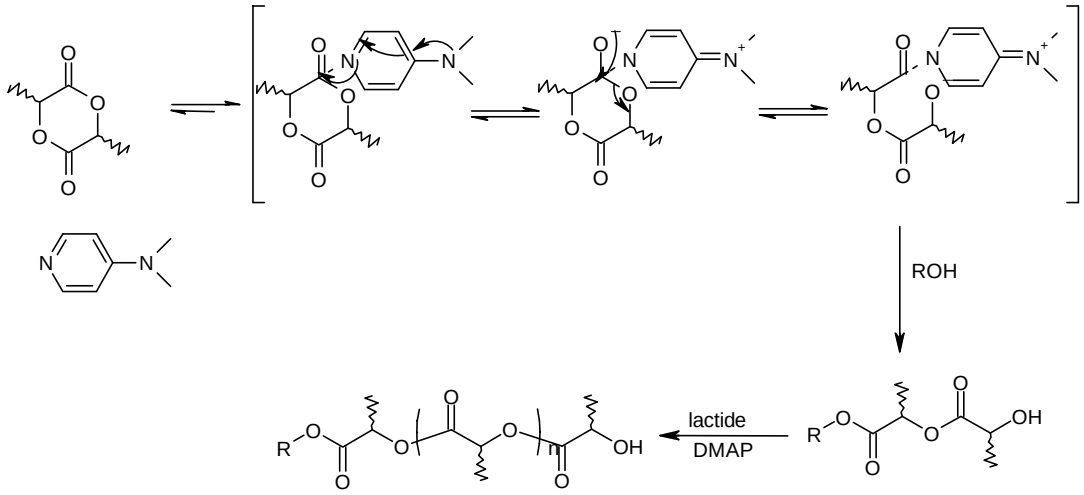


Figure 1.3.1. DMAP catalysed ROP of lactide.

DMAP catalysed reactions require an alcohol initiator for any reaction to proceed, the reaction rate is dependent on the ratio of catalyst to initiator [32, 33]. An excess of 4:1 in catalyst produces the most desirable reaction rates, (although that may not be ideal for short chain compounds as large amounts of catalyst would be required to produce the desired products. Traditionally DMAP reactions have been carried out in a solvent (dichloromethane or toluene) as DMAP, lactide and PLA are all soluble in these. However it is possible to use DMAP in a melt reaction at 130 ^{o}C and initial results suggest that the reaction can be complete in 5 to 20 minutes. The amount of time for which the reaction is run in a melt polymerisation becomes very important with the DMAP catalyst as it rapidly catalyses the transesterification reaction between polymer chains [34].

Hedrick *et al.* investigated the transesterification with the idea of using it as a method to control molecular weight and end groups. This is interesting with regard to the preparation of surfactants as they observed that, during the reaction, primary alcohols in the presence of DMAP resulted in chain scission and addition of the

alcohol to the carboxylic acid chain end. Secondary alcohols resulted in no chain scission, but act as good initiators for PLA production. This could offer another method of integration of long chain primary alcohols into PLA. It would perhaps be useful in regards to the costs of PLA relative to lactide. Instead of using lactide as the starting compound you could react PLA with a primary alcohol. However, as only a primary alcohol can be used this is rather limiting to the molecules that can be added to produce different functionality, for example, you could not react with tartaric acid, although sugars such as dextrose, sucrose and sorbitol could be functionalised at only the primary alcohol positions.

1.3.2 N-Heterocyclic Carbenes as Organocatalysts.

The use of N-heterocyclic carbenes as catalysts in ROP of lactide [35] is an interesting recent development. The initial synthesis by Arduengo has opened up a whole branch of chemistry dedicated to the exploration of these compounds as ligands and as catalysts and their chemical reactivity and versatility have become well documented. Among their uses is as replacement ligands for phosphines in organometallic catalysis, where the carbenes have been recorded as enhancing catalytic stability and reactivity. One of the major problems, however, is the difficulty in isolating these carbenes as they are extremely air and moisture sensitive. The in-situ formation of triazolium carbenes [36], from their respective salts has already been used in asymmetric catalysis in the Stetter and benzoin condensations. The ROP of lactide using N-heterocyclic carbenes is shown in Figure 1.3.2.

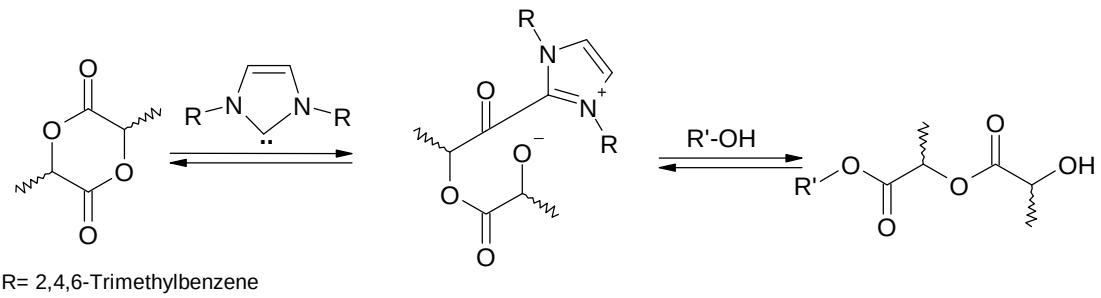


Figure 1.3.2. N-heterocyclic carbene catalysed ROP of Lactide.

From the experimental data, it can be seen that substituent groups had an effect on the catalytic activity. It was noted that chlorination at the 4,5 positions of the imidazolium ring, led to a reduced conversion rate. The conversion had dropped

from 97% to 85%, which indicated that the catalyst could be tuned electronically by substituent effects on the ring. It was further demonstrated, that carbene catalysts could be used to generate lactone/lactide block co-polymers. What is also interesting is that the process is essentially biphasic. The in-situ production of carbenes from the ionic liquid, leads to the carbenes migrating to the organic layer (THF in this case) where the reaction occurs. The pre-catalyst regeneration terminates the polymerisation, i.e. the ionic liquid drops out of the organic phase. This means that PLA can be produced without the active catalyst being present in the final product.

The N-heterocyclic carbene approach is important, as it is the first organocatalytic approach that has a profound effect on the stereochemistry of the PLA. Since R can be modified to add more steric bulk, this can be used selectively to control the tacticity of the PLA polymer. Increasing steric bulk can also reduce the potency of the catalyst, and reduces the reaction rates.

1.3.3 Thio urea-Amine Catalyst for use in ROP of Lactide

Following on from Hedrick's carbene work he investigated one other notable catalyst system using a thiourea-amine catalyst [37], the mechanism is shown in Figure 1.3.3a.

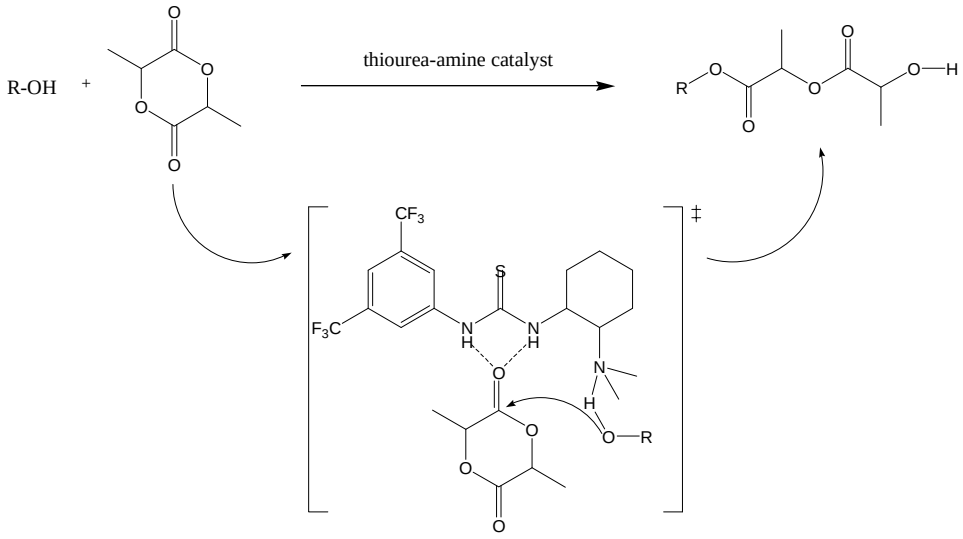
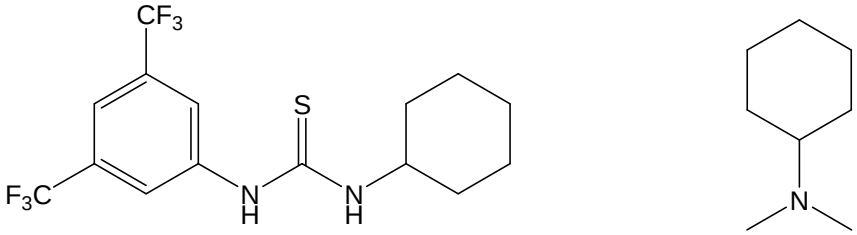


Figure 1.3.3a. The mechanism showing the catalyst activity through intermediate with H-bonding.

To elucidate the mechanism they studied the bifunctional nature of the catalyst, by looking at the catalytic activity of mixtures of its various components see Figure 1.3.3b. In experiments where i and ii were used separately no polymerisation was observed. However, when used together they produced PLA with very good PDI, (M_n = 12,500 and PDI = 1.1). This indicated the bifunctional nature of the catalyst was the most important aspect. In order to prove the hydrogen bonding had a significant role the polymerisations were carried out in a range of solvents both hydrogen bonding and non-hydrogen bonding. Polymerisation only occurred in the non-hydrogen bonding solvents, toluene, chloroform and dichloromethane.



i ii

Figure 1.3.3b. Structure of the separate components within the thiourea-amine catalyst.

Although this catalyst was shown to be highly selective and produced polymers of low polydispersities, it was also less active than DMAP catalysts or most organometallic catalysts, though its long term usefulness as a lactide polymerisation catalyst may be interesting in the production of PLA and copolymers with well defined molecular architecture.

1.3.4 Acid Catalysed Methods

PLA can also be produced using protic acids, however the conditions are not very mild and the PLA alcohol end groups may dehydrate, to form vinyl end groups. A recent work by Pohl *et al.* [38] used trifluoromethanesulfonic acid (triflic acid) and methyl trifluoromethanesulfonate (methyl triflate). In an early study on the polymerisation of β-lactones using sulphuric acid only low molecular weight oligomers were reported, this was probably due to rapid dehydration of the end groups. In the study by Pohl *et al.* they never mentioned the formation of vinyl functions although this may be attributed to the high molecular weight polymers produced, as they were working at ratios of 60:1. In this case the minor vinyl-

terminated products would probably not appear clearly in the NMR spectrum. Methyl triflate does not require an alcohol initiator as the methyl group migrates to a carbonyl carbon to form a cationic species. The triflic acid and alcohol mechanism is illustrated in Figure 1.3.4.

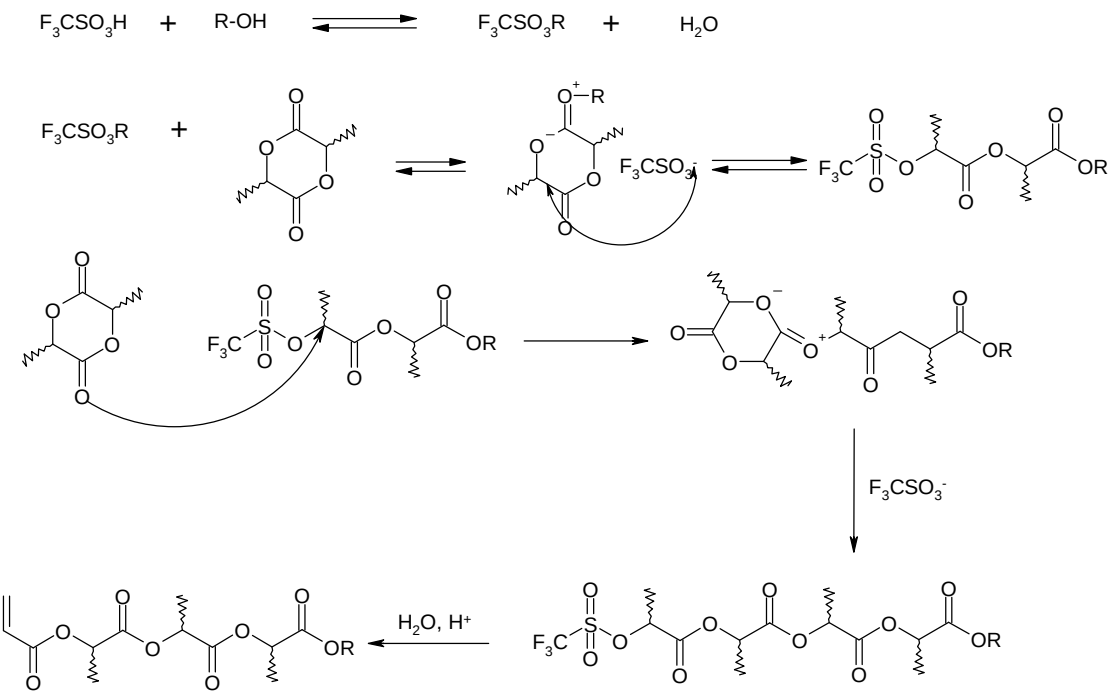


Figure 1.3.4. Triflic acid catalysed ROP of lactide and possible side reactions (3).

The above mechanism 3 was suggested by Kricheldorf *et al.* [39] and it was their observation that polymerisation occurs through triflate ester end-groups rather than free carbeniun ions. Propagation begins with cleavage of alkyl-oxygen bond of the positively charged ring by S_N2 attack of the triflate anion. The triflate-ester end group then reacts with another lactide molecule again in an S_N2 reaction to yield a positively charged lactide that is open. The triflate anion then attacks and opens another charged lactide and polymerisation proceeds.

The dehydration step, if carried out quantitatively may be useful in regards to the preparation of co-polymers where the double bond can then undergo addition (free-radical) polymerisations. This has possible uses for tailoring the structure of the polymers to add branching, or in the case of producing surfactants to add other functionality whether it is hydrophilic or hydrophobic. However, it is unlikely to be

achieved as the acid is likely to cleave at any point along the chain resulting in hydrolysis of the ester groups.

A far simpler method of incorporating a vinyl group into the polymer would be through reaction with a cyclic ester containing the vinyl function as this would react quickly under the reaction conditions and give a vinyl group. A vinyl end group could not be produced through this method as it would stabilise as a ketone, but a C=C in the middle or vinyl branch would be plausible and could be used as a method of producing graft (comb) copolymers.

1.4 "Green" Developments in PLA Production

Studies by Howdle *et al.* [19,20,33] has shown that PLA can be synthesised using supercritical carbon dioxide ($ScCO_2$) as a solvent. The catalyst systems employed so far have been stannous octanoate and DMAP as they are well established and have good solubility in $ScCO_2$. $ScCO_2$ has attracted a lot of attention in green chemistry over the last few years as it removes the need for organic solvents. $ScCO_2$ is a useful solvent as altering the pressure of CO_2 in the reactor can vary its solubility properties. This is useful in polymerisations for continuous flow processes as theoretically the polymer can drop out of the solvent at a certain molecular weight. The use of these reactions requires a stabilizer (surfactant) to help in solubility etc. This also offers flexibility regarding the catalyst. These reactions proved to be interesting in that they produced PLA where the morphology was profoundly altered as a result of the solvent reaction conditions. They were able to produce polymers of poly(lactic acid) and poly(glycolic acid) that were fine powders or micro-spheres, which are a good starting point for the processing of these polymers.

There is also the possibility that ionic liquids could be employed as catalysts for the ROP of lactide using an alcohol initiator. A study of the O-acetylation of alcohols and carbohydrates in 3-ethyl-1-methylimidazolium dicyanamide [emim][dca] and its butyl counterpart [bmim][dca] [40], showed that the ionic liquid acted as a catalyst in the acetylation of α-D-glucose, *t*-butanol, cyclohexanol and various sugars by acetic anhydride. The mechanism of the reaction is still under investigation but it

was hypothesised that it was promoted by the basicity of the dicyanimide anion. Ionic liquids have also been under investigation for many years as solvents for many catalytic processes. These benefit in the $ScCO_2$ extractions as ionic liquids have zero vapour pressure and as such are insoluble in the medium. This would mean that the ionic liquid as the catalyst would not be leeched out, but whether or not a continuous flow system is possible would depend on the relative solubilities of lactide and PLA within these solvents.

1.5 Surfactant Behaviour and Structurally Interesting Copolymers of PLA

Surfactants are among the most important industrial chemicals known and can take on almost any form imaginable. Among the most common uses of surfactant molecules are as detergents in cleaning, in motor-oils, in pharmaceuticals, in the drilling muds used in oil wells and as flotation agents in processing of ores [41]. Surfactants have been investigated intensely for decades and utilization and development of suitable agents for particular purposes is still somewhat of a hit or miss ordeal.

A surfactant is defined as “a surface-active substance that when present in low concentrations in a system, has the property of adsorbing onto the surfaces or interfaces of the system and of altering (to some degree) the interfacial free energies of those surfaces or interfaces.” [41].

The interfacial free energy is the minimum amount of work required to create the interface. When looking at surfactants, the surface tension and critical micelle concentration (CMC) are the most useful data, in terms of surfactant characteristics. The CMC comes about from an expansive series of variables and is at best only a relative term depending on the system it is in, but what is key to understanding this, is the surfactant structure.

1.5.1 The Traditional Surfactant

The most important aspect of producing a surface-active molecule is the structure. The traditional surfactant, consists of a long hydrophobic tail and a polar hydrophilic head, as seen in figure 1.5.1a. To understand the role of copolymers in surfactant chemistry it is first important to understand the basis of micelle formation. The properties of surfactants arise as a direct consequence of the lyophilic (hydrophilic) groups although the structure of the lyophobic (hydrophobic) groups and modifications thereof, may have a greater or less pronounced effect. There are eight common hydrophobic types [41]:

1) Straight-chain alkyl groups of between C_8 to C_{20}.
2) Branched-chain alkyl groups of between C_8 to C_{20}.
3) Alkylnaphthalene residues with C_3 and greater alkyl substituents.
4) Rosin derivatives (rosin is a natural compound found in plant - mainly pine resins)
5) High molecular weight propylene oxide polymers e.g. polyoxypropylene glycol compounds.
6) Long-chain perfluoroalkyl groups ($C_nF_{2n+1}X$; where X is the corresponding hydrophilic portion or other related groups.)
7) Polysiloxane groups ($-[SiO(R)_2]_n-$).

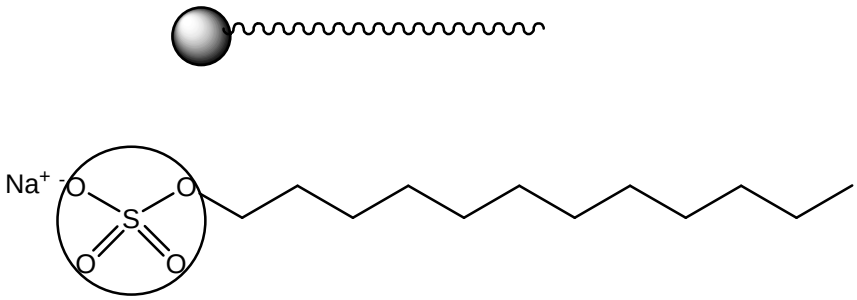


Figure 1.5.1a. Shows a simple common surfactant sodium lauryl sulfate, which is of the traditional model of surfactant molecule.

The main reason for this is down to the role they play in the drive behind self-assembly of micelles. When considering how a surfactant is best used micellization [41] plays a very important role. It is important since interfacial phenomena such as detergency and solubilization are directly dependent on the formation of micelles in

solution, however, micelle formation also indirectly affects surface and interfacial tension reduction.

For most considerations micelles are thought of as spheres where the interior contains hydrophobic groups with the polar ends facing outwards forming the exterior of the micelle as illustrated in figure 1.5.1b

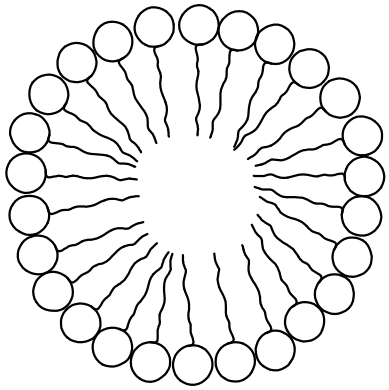


Figure 1.5.1b Cross-section representation of micelle, with ionic head group and hydrophobic tail.

Altering the temperature, concentration of surfactant and addition of additives can lead to changes in the aggregation number of micelles and can change their size and shape. The structure of a micelle can be anything from spherical through to rodlike or disklike to a lamellar shape.

As well as the linear polymers of lactic acid there has been a lot of interest in the formation of co-polymers of PLA. Copolymerisation is becoming popular due to it being a useful method of tailoring the physical properties of the polymer. In most cases copolymerisation is carried out with other biorenewable/biodegradable polymers and is usually formed in a multi-step process. The largest market for copolymer production is for use as drug delivery systems and in production of sol-gel materials. Therefore the surfactant properties of these copolymers are of greatest interest.

Due to a great depth of available hydrophobic types, this will be of considerable interest in the development of the poly(lactic acid) alkyl esters. However, going by the criteria of green chemistry and the need for natural feedstocks and the biodegradability we need to look at the hydrophobic groups in terms of their

effects on nature. The straight and branched chain alcohols can be derived from natural sources as can alkylnapthalene compounds. Propylene oxide polymers however, are still reliant on the petrochemicals industry and perfluoroalkyl groups are synthetic compounds that are the subject of some debate as to whether they are environmentally benign.

The copolymers that have been investigated include di-block, multi-block and star shaped copolymers. The simplest method of producing co-polymers is to use a polymer with alcohol terminal unit and use this as the alcohol initiator in a ROP of lactide. In the synthesis of multi-block copolymers they have carried out ROPs with several other cyclic esters other than lactide including glycolide and ε–caprolactone.

Much of the interest has been in the production of co-polymers for use in biomedical applications. Isotactic poly(lactic acid) can be brittle and not ideal for use as sutures or drug release devices, so by copolymerising they can produce a more flexible material, which is biodegradable and biocompatible. There are also copolymers of the different conformations of PLA, some work has been done on PLA isotactic-heterotactic and stereocomplex copolymers [42, 43].

The other main benefit in copolymers is in producing a plastic that is easier to process, as this is often a limiting factor in how a material may be used for certain applications. Poly(L-lactide)-poly(ε-caprolactone) multi-block copolymers and their properties have been studied [44]. These were formed in a multi-step process to form multi-block, tri-block and random copolymers. Among one of the steps was the formation of a carboxylic acid end group by reaction with succinic anhydride.

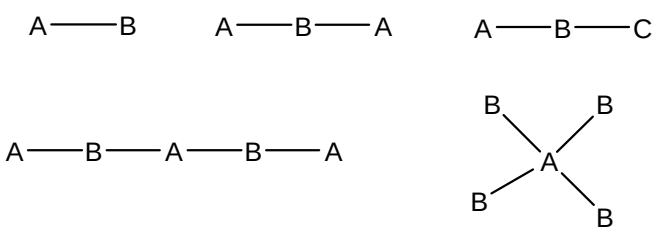


Figure 1.5.1c Basic Structural Templates of Common Co-Polymers

All of these structure types can play some role in surfactant molecules and emulsification behaviour.

1.5.2 Di-block and Alternating Multi-block Copolymers

It is well reported in the literature that AB di-block copolymers when dissolved in a solvent that is good for A and poor for B (or vice-versa) and at concentrations above the CMC, form micelles [45]. It is also known, that when solid particles e.g. TiO_2 are added to the solution, adsorption onto the solid surface can take place leading to the formation of a polymeric layer. This leads to polymer brushes of the non-adsorbed branch of the polymer, stretching out into solution and as such these have found application in dispersed systems to enhance stability [41].

There are many examples of di-block copolymers, some of which are discussed in this report. In essence poly(lactic acid) long chain alkyl esters from long chain alcohol initiators are di-block copolymers. Much of the other work has featured polylactide-co-glycolide.

Tolman *et al.* have produced a perfectly alternating copolymer of lactic acid and ethylene oxide [46]. In this study they did not use lactide as the reactant and benzyl alcohol was used as the initiator species. They instead carried out the ROP of 3-methyl-1,4-dioxane-2-one (MDO) as the reactant, which is a cyclic ester anhydride containing one lactic acid unit and one ethylene oxide unit (Figure 1.5.2a).

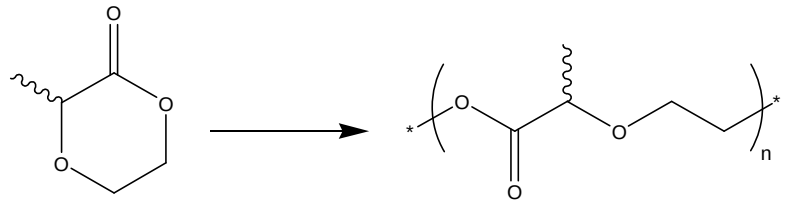


Figure 1.5.2a. Reaction Showing MDO to Copolymer of lactic acid and ethylene oxide.

A study by Lowman *et al.* [47], used mPEG-PLA poly(lactic acid-co-methoxypolyethylene glycol) copolymer to produce prodrug micelles. A prodrug micelle is where a drug molecule is grafted onto the hydrophobic part of the molecule and this becomes the core of the micelle. This polymer encapsulation means that the drug is not released until it reaches the correct part of the body – or is slowly released

over a long period of time. This was a very interesting and unusual multi-step synthesis where methoxypolyethylene glycol was first reacted with succinic anhydride and the carboxylic chain end was then used to initiate ROP of lactide to produce a PLA with a carboxylic acid terminus. The synthetic pathway is shown in figure 1.5.1b, in most cases these steps would be done in reverse, i.e. mPEG would be reacted with lactide followed by ring opening termination with succinic anhydride to produce the carboxylic acid chain end. However, succinic anhydride is more hydrophilic than PLA and could interrupt the polymer's ability to form good micelles.

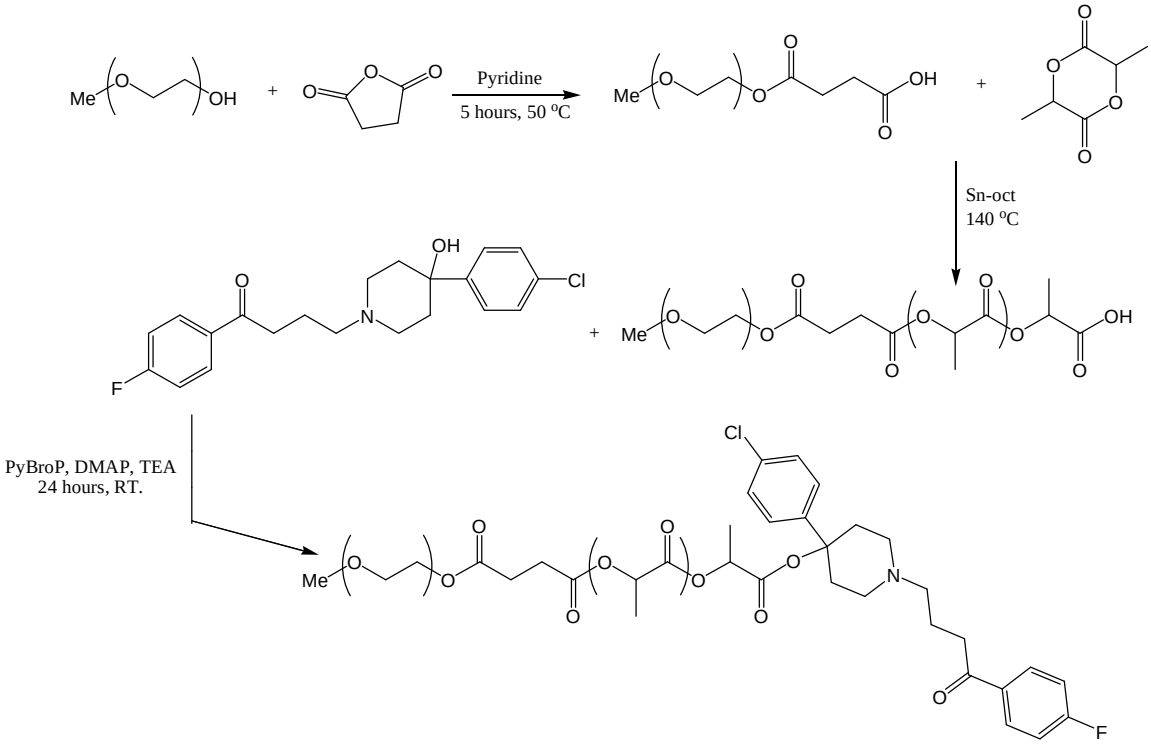


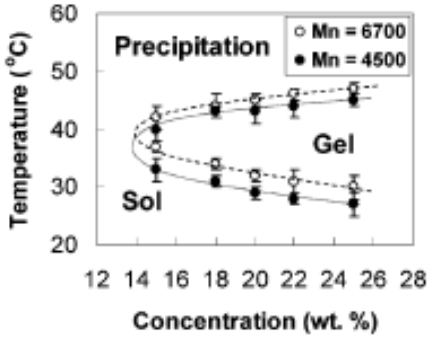
Figure 1.5.2b Synthesis of mPEG-PLA Prodrug.

Polyethylene glycol offers a simple method of producing A-B-A alternating co-polymers as it has alcohol groups at either end.

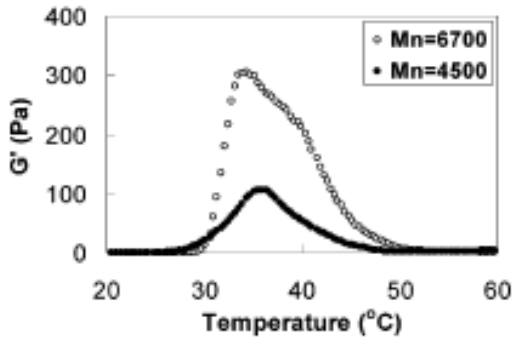
The structure of A-B is atypical of most polymeric micelles. Where A might represent the hydrophilic portion of the molecule (possibly PEG) and B is the hydrophobic portion of the molecule PLA or PεCL (poly ε–caprolactone). Of PEG co-PLA has become an important molecule in the production of sol-gel materials, where in the presence of water the polymer swells forming a stable gel.

Alternating multi-block copolymers have produced considerable recent interest due to their Sol-Gel behaviour, which may be thermally reversible in some cases. In a recent study Jeong *et al.* [48] investigated the sol-gel behaviour of PEG-PLLA copolymers with an M_n between 4500 and 7800 Daltons. In these cases 1,6-hexanediol was used as initiator and the PLLA ends were reacted with succinic anhydride to produce the carboxylic acid ends. The multi-bock copolymer was formed by coupling the carboxylic acid chain ends with PEG_{600} using a DMAP catalyst and dicyclohexylcarbodiimide (DCC) in DCM at RT for 24 hours. The low reaction temperature inhibits transesterification and DCC acts as a water scavenger preventing the reverse reaction from occurring.

From their research they noted that at M_n values above 7800 Daltons the copolymer precipitated, but at M_n of 6700 and 4500 surfactant materials with a CMC of 0.008 wt % were produced. A Sol-Gel transition occurs at 15 wt % where high amounts of aggregation lead to the micelle diameters over 100 nm at 30 to 45 ^{o}C; the effect of this is a gelation window that incorporates body temperature 37 ^{o}C where a semi-solid is formed. The graphs below (Graphs 1.5.2c and 1.5.2d) show the effect of M_n values on the sol-gel transitions and the gelation storage modulus in aqueous media.



Graph 1.5.2c Showing the sol-gel transitions function of temperature and concentration



Graph 1.5.1d Shows the storage as a modulus of sol-gel materials

As can be seen copolymer with M_n = 6700 has a higher storage modulus and is thus a more stable and solid gel. The gelation was tested *in vivo* and *in vitro* and the authors conclude that this could be used in drug delivery as it can be injected into the area of the body and quickly form a stable gel allowing slow release of the drug.

1.5.3 Tri-block Copolymers of A-B-C Variety

A tri-block co-polymer of poly(ethylene glycol)-*b*-poly(L-lactide)-*b*-poly(L-glutamic acid) has been synthesised recently [49]. This copolymer is interesting as it was created to combine hydrophobicity and hydrophilicity but with the idea of being a candidate for drug delivery. Through drop shape analysis (contact angle measurements) they saw that the poly(ethylene glycol)$_{750\text{-}2000}$ and poly(L-glutamic acid)$_{3000\text{-}13800}$ were the hydrophiles, PLLA$_{2800\text{-}3400}$ was the hydrophobe. They looked at the effects before and after deprotection of the glutamic acid to the carboxyl terminal and found that with high MPEG and PBLG to lactide, the contact angle was reduced.

Therefore by co-polymerising, the nature of the surfactant can be altered to have better end-group surfactant ability or in altering chain lengths and shape we can alter the way micelles are formed.

As well as altering the micelle shape etc. copolymerisation may also give control over the physical properties of the polymer. By copolymerising with non-linear polymers the hardness/viscosity of the polymer can be reduced, thus producing a more liquid like surfactant. It also has the possibility of tailoring different combinations of hydrophile - hydrophobe combinations, offering different ways to utilise the surfactant and altering the way micelles form.

As well as copolymerising it may be possible to use further ROP of a cyclic anhydride to stop the reaction, as transesterification can be inhibited by removal of terminal alcohol groups. If you use, for example glutaric anhydride or more reactive succinic anhydride these molecules ring open to form carboxylic acid termini, under the conditions of the reactions (with exception of strong base) this would prevent further ring opening at lactide or transesterification between polymer chains occurring. Carboxylic acid groups have much better surfactant behaviour than alcohols; better H-bonding and can also form the basis of anionic surfactants. As well as reaction with anhydrides it may be possible to react other cyclic compounds to produce different functionality, (for example a vinyl group) through this methodology.

1.5.4 Star-shaped Copolymers

Star-shaped or miktoarm copolymers are perhaps the most interesting in term of their surfactant properties as they have been of considerable interest over recent years in terms of their micellization properties and architecture [50]. As the name suggests star-shaped copolymers are polymers that branch out from a source, in the case of lactide these are produced from the reaction of polyols with lactide. There is some mention in the literature of lactide star-shaped copolymers, although it is a somewhat less focussed on area.

It has been long established that block co-polymers can self assemble into micelles under the proper solvent conditions, the micellization properties of miktoarm star copolymers are somewhat less established. A paper by Radke *et al.* [51] looked at the chromatographic behaviour of poly-lactide star-shaped copolymers by tailoring the properties by esterification of primary and secondary alcohols attached to the core and on the number of lactide chains. They used polyols containing 1-6 OH groups and catalysed reactions with $Sn(oct)_2$. They concluded that increasing the number of functional O-H groups leads to a stronger interaction with the stationary phase and thus increases the retention volume, the increase in the number of arms (keeping number of functional O-H groups constant) results in a minimum retention volume at 4 arms.

Shi *et al.* [52] have looked at different methods of producing ABC star and tri-block copolymers by a combination of ROP and reversible addition-fragmentation transfer (RAFT) polymerisation using a bifunctional macro-transfer agent. In their work they looked at producing poly(ethylene oxide) methyl ether/polystyrene/poly(L-lactide) ABC miktoarm star copolymers. To produce the final product required 5 steps, the first being the reaction of MPEO with maleic anhydride. The product was obtained in 96 % yield. The next step was the reaction of MPEO-MAh with dithiobenzoic acid, after which it was reacted with polyethylene oxide. The next step was to RAFT polymerise with styrene using azobisisobutyronitride (AIBN) as initiator. The final step was ROP of lactide using the terminal OH of the polyethylene oxide as initiator and stannous octanoate as catalyst. The RAFT polymerisation should be carried out before the ROP as under ROP conditions some of the

dithiobenzoate groups could be lost, but hydroxyl groups are not lost under RAFT conditions. As yet the self-assembly properties (formation of micelles) of this polymer system have not been reported.

Jada *et al.* [53] prepared a tri-arm star-block copolymer based on polystyrene, poly(ethylene oxide) and poly(ε-caprolactone) and looked at its adsorption properties at the solid-solution interface. In this study they were looking at the adsorption of their tri-block star copolymer onto TiO_2 surfaces, they found that poly(ethylene oxide) plays an important role in anchoring the polymer to the surface and that poly(ε-caprolactone) forms the surface layer with polystyrene branching freely into solution.

1.6 Evolution of Ideas

The work discussed previously has shown how PLA can be prepared and the different types of PLA structures that can be obtained by choosing the right initiator and catalyst combination. For the work that is to be discussed in the chapters to follow the focus had to be directed towards an end result, which was to produce molecules that were surface active and could possibly be used as emulsifiers. In terms of polymer structure the first idea was to go along the traditional surfactant route of an A-B type copolymer, where a long chain alcohol would be employed as the initiator. For the catalyst there were numerous options available. The choice of tin (II) ethylhexanoate and DMAP were down to two main factors:

1) They had different catalytic mechanisms and could be used for different reactions.
2) The tin (II) catalyst is approved for use in food, pharmaceutical applications etc, therefore the issue of toxicity is not a problem.

The idea of creating a new catalyst system for these reactions based upon metal alkoxides of long chain alcohols was considered. However, given the original project was to be an M.Phil the time constraint and the industrial funding aspect meant that looking at the polymer structure itself and physical properties was a better use of time. That is not however to say that the work has not developed any interesting catalyst ideas for producing surfactants, but this will be discussed in due course.

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Chapter 2

Analytical Techniques for the Elucidation of Poly(lactic acid) Based Polymers and Surfactants.

2.0 Aim

The aim of this chapter is to illustrate the different analytical techniques required for polymer and surfactant testing, giving details of how they work and why they are important in the elucidation of polymer structure as well as for defining polymeric physical properties.
This chapter will discuss in some detail polymer analysis using:

1) Nuclear Magnetic Resonance Spectroscopy (NMR)
2) Electrospray Ionisation Mass Spectrometry (ESMS),
3) Matrix Assisted Laser Desorption Ionisation Time Of Flight Mass Spectrometry (MALDI-TOF)
4) Gel Permeation Chromatography (GPC)
5) Differential Scanning Calorimetry (DSC),
6) Thermal Gravimetric Analysis (TGA) – (water uptake analysis)
7) Wilhelmy-Plate Surface Tension – (determination of CMC and surface tension)
8) Travelling Angle Goniometer for contact angle measurement.

2.1 Polymer Characterisation by Nuclear Magnetic Resonance

The first important tool used by the polymer chemist is NMR spectroscopy. For large polymer molecules – it is perhaps a less robust method as relative intensity of the repeat units means that the initiator and/or end groups may be difficult to locate, but running at higher frequency and increased scans can compensate for this. ^{1}H NMR spectrometry can be used to determine important characteristics of polymers such as number average molecular weight (M_n) by end group analysis and information

on the polymer's tacticity. ^{13}C NMR spectroscopy is an important method and may be used to determine the tacticity and, in the case of the polymers to be discussed, to determine whether the initiator is attached to the polymer and whether there are any structural unit anomalies.

2.1.1 End Group Analysis.

End group analysis by ^{1}H NMR spectroscopy is a simple method used to determine the M_n value for the polymer. It gives an indication as to how successful the polymerisation has been as the M_n value should be close to the predicted M_n from the polymer to initiator ratio. The ^{1}H NMR spectrum can also be used to determine how much lactide starting material has been consumed.

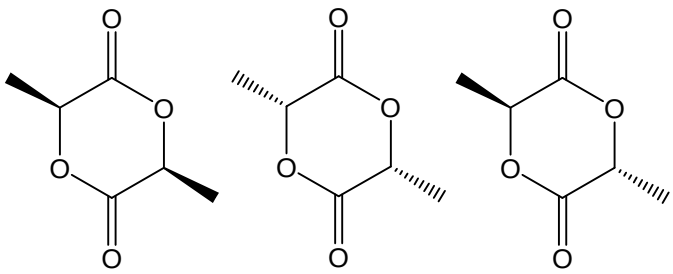
In some cases an internal standard may be used to aid end group analysis. This is usually tetramethylsilane (TMS) as it has peak at 0 ppm, the internal standard gives an indication as to how much lactide starting material has been consumed. This is especially useful for high molecular weight PLA and high molecular weight PLA copolymers. End group determination is carried out by comparing the integral peak size of the proton from the methine (C**H**(CH_3)OH) 4.35 ppm end group and the methine groups from along the polymer chain (C**H**(CH_3)O) 5.2 ppm. Using a simple equation:

$$Mn = \frac{P}{E} + 1 \qquad (1)$$

Where P is polymer integral height and E is the end group integral height.

2.1.2 Polymer Architecture and Tacticity

NMR spectrometry is the most useful method for looking at the tacticity and molecular architecture of a polymer. This is very important in the synthesis of PLA as there are several isomeric forms (shown in Figure 2.1.2a) of the starting material due to the presence of stereogenic centres.



L-lactide D-lactide *meso*-lactide

Figure 2.1.2a shows the different enantiomers of lactide, L, D and meso.

As well as the enantiomerically pure forms, lactide is also commercially available as the racemate D,L-lactide. The difference in the stereochemistry results in different polymer tacticities that in turn result in different physical properties. D and L-lactide lead to the formation of isotactic PLA that is characterised as being crystalline, hard/brittle and optically opaque. The D,L-PLA however is syndiotactic, optically transparent, less brittle with less order. Details of the tacticity can be gathered from ^{1}H NMR and ^{13}C NMR spectroscopic studies as well as HETCOR (2D heteronuclear correlation experiments). Accurately to define the tacticity, the assignments are usually given in the form of tetrad sequences; the tetrad sequences are shown in Figure 2.1.2b.

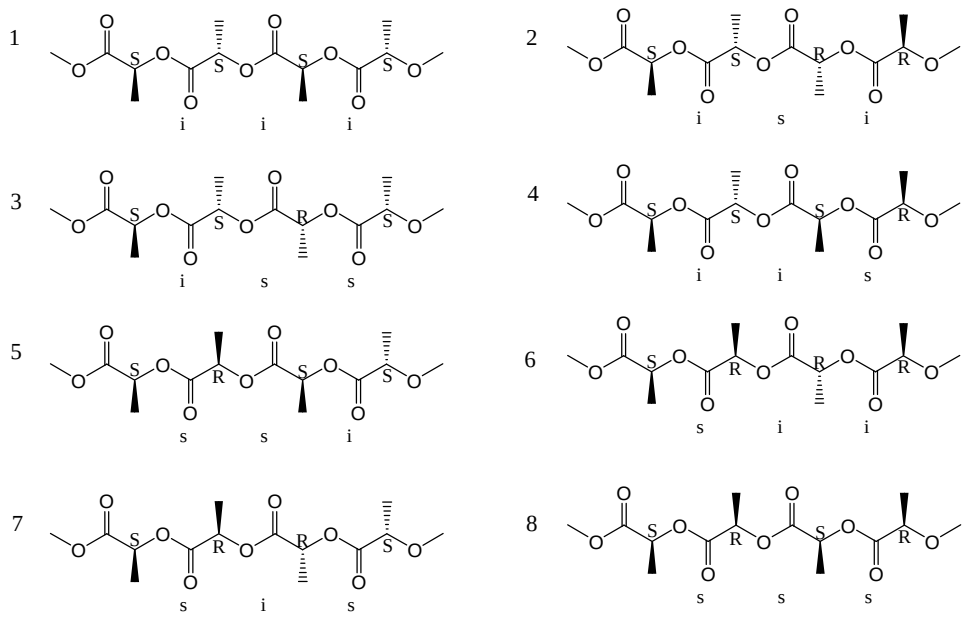


Figure 2.1.2b shows the tacticity of the PLA tetrads. 1) represents an isotactic sequence only possible with enantiomerically pure lactide. 8) shows a syndiotactic sequence only possible with meso lactide. 2-7 are tetrad sequences produced from D,L-lactide or by racemization of D and L lactide.

Tetrads are blocks of 4 lactic acid units that have a defined stereochemistry along the chain where each pair are defined as either isotactic or syndiotactic which leads to an overall polymer sequence. There has been debate among the scientific community as to how these sequences relate to the intensities shown on the ^{1}H NMR spectrum. The common approach to assigning tetrad sequences is to use NMR spectra and Bernoullian statistics. Much of the subsequent determinations are based on work by Kricheldorf [1]. Subsequent work by Kasperczyk [2] used ^{13}C NMR and the statistical approach for assigning the spectra of PLA produced where lithium *tert*-butoxide was used as a catalyst. Figure 2.1.2c shows the methine carbons of their defined tetrad sequences.

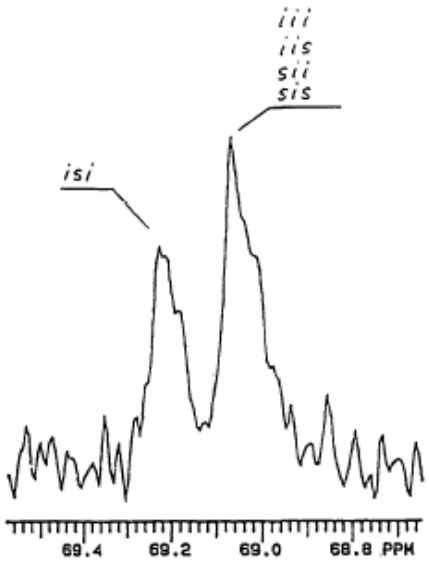


Figure 2.1.2c Shows the tetrad sequence for methine carbons taken at 75 MHz at 303 K for *rac*-PLA [2].

However, there have been several groups who have challenged the older interpretation methods and proposed other tetrad assignments. Chisholm *et al.* [3] using HETCOR experiments proposed new tetrad assignments for *rac*-PLA as well as assignments for *meso*-PLA. Figure 2.1.2d shows the old assignments along with the assignments they now propose based on their 2D NMR experiments.

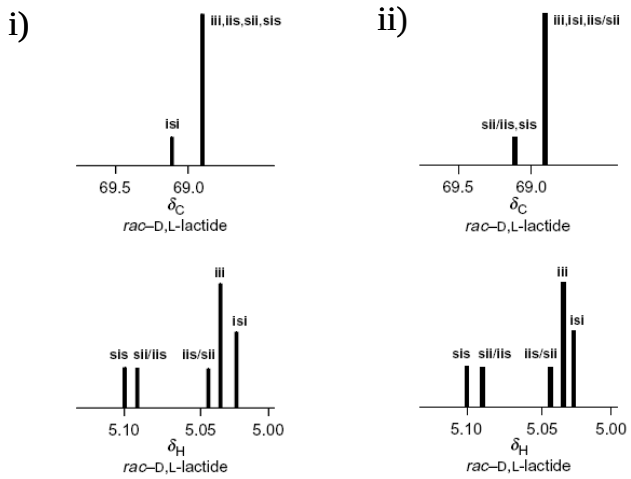


Figure 2.1.2d i) shows the originally proposed tetrad sequences from ^{13}C and ^{1}H NMR, ii) shows their proposed tetrad sequences [3].

These were determined at a variety of field strengths from 400 to 750 MHz for ^{1}H NMR spectra. Due to Bernoullian statistics iis and sii are considered as equivalent, which may lead to some ambiguity as to their overall position on the spectrum.

However the main disagreement here seems to be the position of the isi tetrad in the ^{13}C NMR spectrum, which is resolved by 2D NMR studies. A more recent paper by Munson *et al*. [4] strived for a more unambiguous approach to determining PLA stereo sequences. They again used the HETCOR in conjunction with HMBC and HMQC experiments with selective ^{13}C labelling. They wished to resolve why Bernoullian statistics and HETCOR experiments give contradictory data for the isi and sis tetrads. Their conclusion was that Bernoullian statistics are unable to account for the differences between isi and sis as they have equal statistical probabilities. Using 2D NMR techniques and previously determined relationships between assignments in the ^{1}H NMR and ^{13}C NMR spectra it was possible independently to assign each tetrad. Figure 2.1.2e shows their corrected tetrad sequences based upon the 2D NMR experiments.

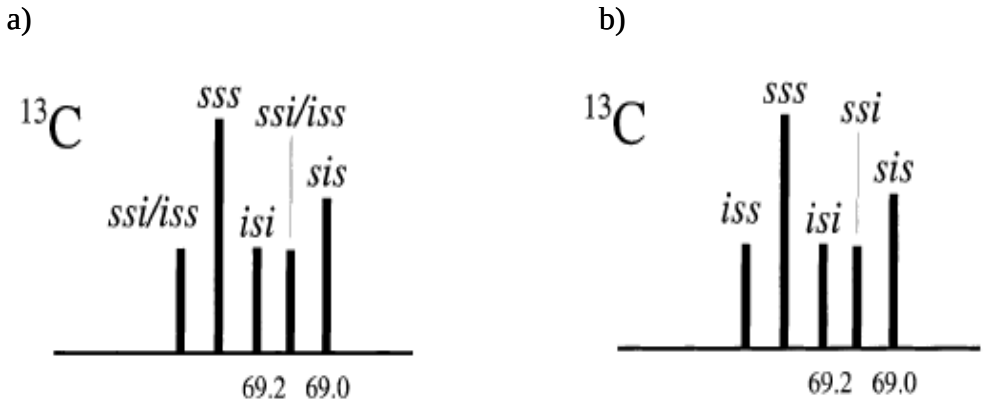


Figure 2.1.2e a) Shows the previously accepted tetrad assignments; b) shows the new modified assignments [4].

2.2.2 NMR Spectrometers used in this Thesis.

All NMR studies were carried out in deuterated solvents on either a Bruker Avance 300 Spectrometer or a Bruker Avance 500 Spectrometer operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR spectra.

2.2 Methods to Analyse Polymer Size and Polydistribution

There is consistent debate over how useful Mass Spectrometry is in polymer analysis. Generally it is not accepted as a method of acquiring M_n or M_w values for polymers. Although some MALDI spectrometers are capable of acquiring these parameters. They are considered most useful as a means of checking polymer repeat units and in lactide polymerisation can be used as a means of determining the amount of transesterification occurring in the polymer. A far more robust approach to determine M_n and M_w values and to ascertain the PDI is to use gel permeation chromatography - and this is by far the widest used analytical technique in polymer chemistry.

2.2.1 ESMS in Polymer Analysis

ESMS or ESI-MS is a rarely used technique in polymer analysis due to its poor resolution of polymer molecular weights above 1000-1500 amu. It can be used fairly well for analysing oligomers. Below is a schematic (Figure 2.2.1a) [5] of how the EIMS works.

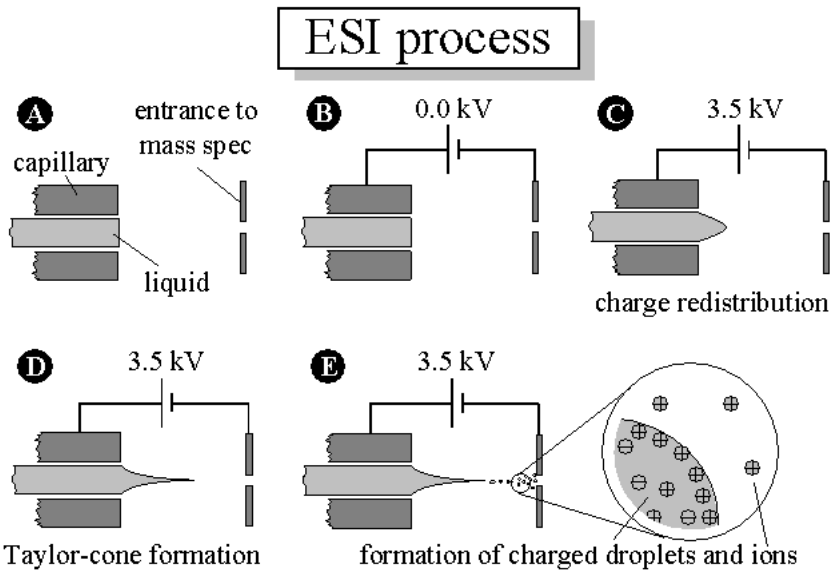


Figure 2.3.1a: Schematic of how a sample becomes an electrospray [5].

First a sample is dissolved in an appropriate solvent (methanol is often used). It is then passed through a metal capillary towards the ionisation source. From the ionisation source a voltage of 3-6 kV, which causes the sample to disperse into highly charged particles, is applied. Nitrogen is used as a nebulising and drying gas to carry the droplets towards the mass spectrometer detector and to cause evaporation of the solvent. The sample ions are then able to pass into the mass analyser where the m/z (mass to charge) ratio is determined and this produces a distribution (usually Gaussian) of molecular weights. Care must be taken using this method as it can often produce 2 spectra. Positive and negative spectra can be formed due to differences in ionisation that occur. The (+) spectrum in the case of PLA shows peaks with M+Na (from Na salts in the matrix), and the (-) shows M-H.

One of the main problems with polymer analysis is that the polymers may often be too heavy to reach the mass analyser – resulting in the low resolutions.

However it still makes it a somewhat useful method of tracking transesterification in a polymer. This is done by looking at repeat unit separation. Since lactide is di-lactic acid anhydride, each repeat unit without transesterification should be 144 amu, however, when transesterification occurs this leads to randomisation within the chain so we see odd numbers of repeat units with 72 separation. This occurs because the growing chain can cut an existing polylactide chain in between lactide units or at the middle of a lactide unit (see Figure 2.2.1b).

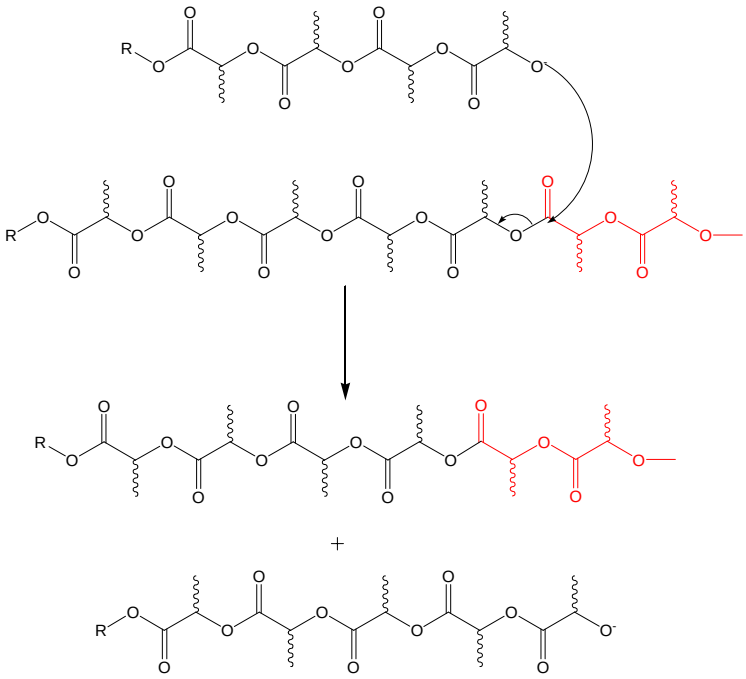


Figure 2.2.1b. The Mechanism by which Transesterification occurs

2.2.2 MALDI-TOF in Polymer Analysis

A far more useful method in polymer analysis is MALDI-TOF mass spectrometry. MALDI is also used to analyse proteins and other macromolecules and is well suited to polymer analysis. In this method the polymer is again ionised, but this time the ionisation is carried out by ionising radiation produced from an intense laser which emits in the ultraviolet (UV) or infrared (IR) region of the spectrum. The polymer is dissolved in a suitable solvent and applied to a solid matrix, which absorbs the particular frequency used by the laser light source. Through the matrix the energy is directed at the sample, avoiding sample decomposition. In order to acquire a good mass spectrum the sample and matrix must have similar solubility properties – thus it allows eventual dispersion of the polymer throughout the matrix, which is important in preventing formation of polymer aggregation. The molecular ions produced from the laser desorption are then able to move through the flight tube, where time of flight takes account of the molecular weights and the data is gathered at both a linear and reflected detector. The process is shown in Figure 2.2.2. [6]

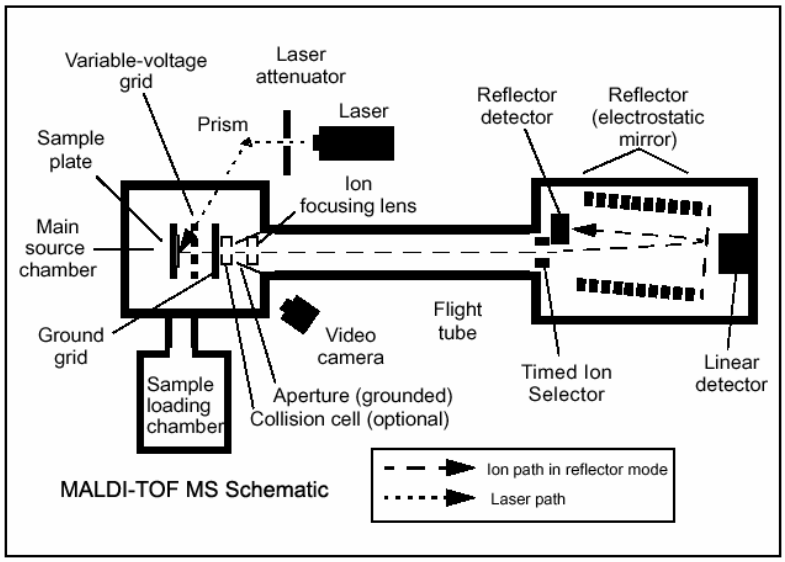


Figure 2.2.2 Schematic showing how MALDI-TOF data is acquired [6].

MALDI-TOF is a far more practical method of deducing the mass spectrum of large and complicated polymers and can be used on samples of Mwt >200,000 Daltons. This is a powerful method at deducing the level of transesterification and is in most cases sensitive enough to give a good indication of the polymer distribution.

2.2.3 Mass Spectrometry to Elucidate Macrocycles

An area where both ESMS and MALDI-TOF mass spectrometry have become very important characterisation tools in polymer synthesis is in the analysis of samples for the production of macrocyclic rings. In condensation esterification or ring opening polymerisation where a catalyst is used that strongly promotes transesterification, ring-chain equilibrium exists. In condensation reactions this occurs when conversion is >96 %, and almost all water is removed from the system. These rings are difficult to analyse by NMR methods and their size cannot be determined, as they have no end groups. However, they show defined molecular weight distributions in MALDI-TOF and ESMS spectra.

In a recent paper by Arakawa *et al.* [7] they used ESMS to analyse the cycles they were forming by the dehydration condensation of L-lactic acid. Since the rings and the linear chains have different m/z peaks, it was possible for them to analyse the

rings and prove that they were able to produce mostly cyclic trimer, with some of the larger rings also (see Figure 2.2.3a).

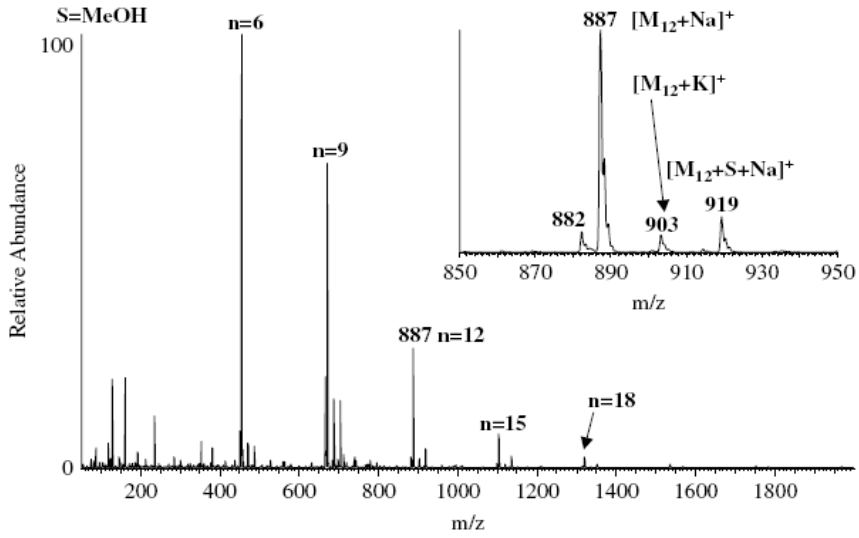


Figure 2.2.3a spectrum of PLA cycles, where trimer is n=6 (3 x dilactic acid) [7].

2.2.4 Gel Permeation Chromatography in Polymer Chemistry.

GPC (also known as Size Exclusion Chromatography) is the most commonly used method in polymer chemistry to obtain information on the molecular weight of polymers. It is also a technique that can be used preparatively to obtain a narrow range of molecular weights. The GPC can be used to determine a wide range of factors about a polymer including; M_n (number average molecular weight), M_w (weight average molecular weight), M_p (peak average molecular weight) and polydispersity index (PDI) which is equal to M_w/M_n [8].

The GPC is special type of column chromatography. The column in this case contains a highly porous material (often a cross linked polymer) that is swollen using an appropriate solvent. The materials are filtered out according to size (hydrodynamic radius) by molecular sieving. In this case however, the polymers with the largest hydrodynamic radii are able to pass through the column first. It is believed that the smaller polymer molecules pack better into the pores of the column and thus pass through slower. The molecular weight fractions are then analysed using one or more techniques including UV and IR detectors and the refractive index. A plot of the

detector response i.e refractive index against the elution volume (V_r) is recorded and in some cases the molecular weights determined by comparing with a polymer standard (polystyrene is often used as it has a approximately the same PDI over a wide range of molecular weights). A schematic of how the GPC and column work is shown in Figure 2.2.4 [8]

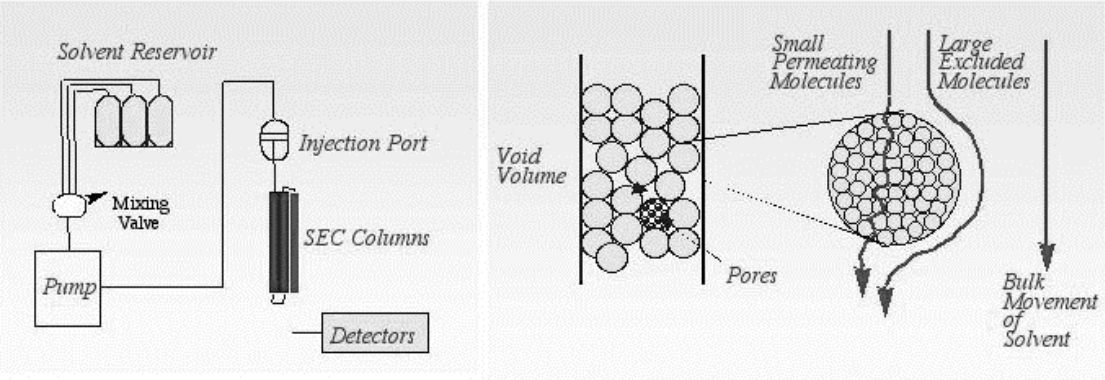


Figure 2.2.4 A Schematic Representation of a GPC and how polymers permeate through the column [8].

2.2.5 Equipment used for Mass Analysis

ESMS was recorded on a Waters, Micromass LCT, Time of Flight mass spectrometer, coupled to a Waters 2975 HPLC all samples were made up in Methanol or Acetonitrile, depending on which gave the best signal.

MALDI-TOF was recorded on an Applied Biosystems 4800 MALDI-TOF where methanol was used as solvent.

Gel Permeation Chromatography was carried out at Nottingham Univeristy using a Polymer Labs LC1130 HPLC pump, two 30 cm PLGEL 5μm mixed-D separation columns, and an evaporative light scattering detector (Polymer Labs PL-ELS 1000). Calibration was achieved by means of polystyrene narrow standards (Polymer Labs). THF was used as the solvent for all polymers.

2.3 Thermal analysis of Polymers

The thermal analysis of polymers is important in determining the physical characteristics of polymers, which are useful in regards to polymer processing. The two most common thermal techniques are Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA). These are both sensitive techniques and require only a few milligrams of sample to obtain results.

2.3.1 The use of Differential Scanning Calorimetry in Polymer Analysis.

DSC is a highly useful method in polymer analysis and gives an understanding of the polymer's physical characteristics by ascertaining at which temperature its physical state changes. Different polymers may have different physical characteristics, but the three most common phase changes recorded are the glass transition temperature (T_g), the crystallisation temperature (T_c) and the melting point (T_m).

The DSC works by heating a sample and reference at the same rate and comparing the heat absorbed or heat produced (heat flow) at a given temperature. As the heat flow is different between the polymer and the reference the heater beneath the polymer sample has to work harder to produce a similar heat flow to the reference. This basically gives information on the heat capacity (C_p) of a polymer as it is heated which varies throughout the polymer's various thermal states. The heat flow is then plotted on a graph by a computer based upon these equations:

$$\frac{\text{heat}}{\text{time}} = \frac{q}{t} = \text{heat flow} \qquad (2)$$

$$\frac{\text{temperature increase}}{\text{time}} = \frac{\Delta T}{t} = \text{heating rate} \qquad (3)$$

$$\frac{q/t}{\Delta T/t} = \frac{q}{\Delta T} = C_p = \text{heat capacity} \qquad (4)$$

The thermal states have different heat flows, which can be endothermic or exothermic. The T_c (crystallisation temperature) is an exothermic transition as heat is

released during the thermal transformation and the T_m (melting point) is an endothermic transformation as heat is absorbed in order to cause the state change. The T_g (glass transition temperature) is a small endothermic process and unlike the T_c or T_m does not give a sharp peak or trough. The T_g represents a small change in the heat capacity that continues through to the other changes in state. A representation of these phase changes can be seen in Figure 2.3.1 [9].

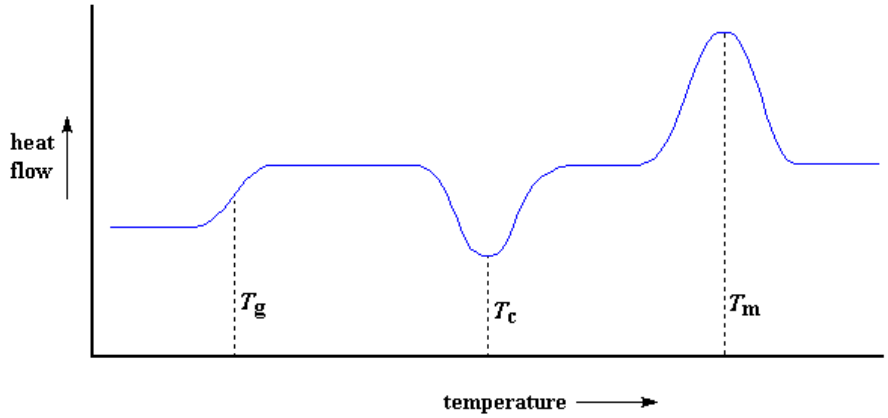


Figure 2.3.1. Shows a characteristic DSC trace indicating where the various phase transitions occur [9].

2.3.2 Thermal Gravimetric Analysis of Polymers and Water Uptake.

Thermal Gravimetric Analysis (TGA) is a method used to determine the thermal stability of polymers or for analysing a polymer or micellar system's ability to retain water. A TGA is a very sensitive mass balance held within a heating chamber, as the sample heats up the mass is recorded over a given time and temperature and the loss in mass is determined as a percentage of the overall starting mass. This gives a good indication as to the thermal sensitivity of a polymer, as physical processing cannot be carried out in a temperature range where the polymer is decomposing. Figure 2.3.2 illustrates a simple TGA trace showing how the mass changes with increasing temperature.

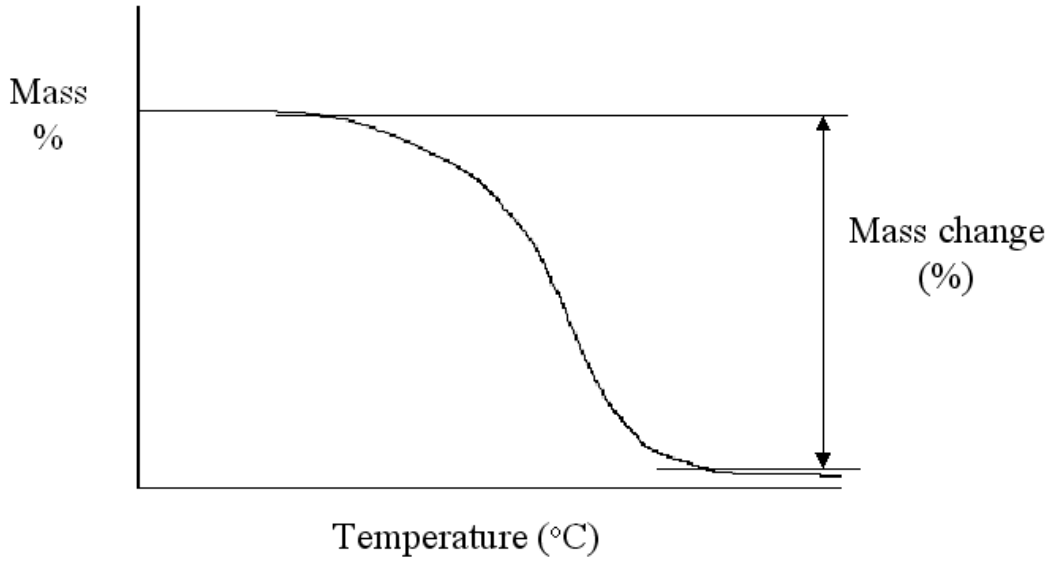


Figure 2.3.2 A representation of a simple TGA trace.

Another related technique is TGA mass spectrometry. It works on the same principle except the TGA is coupled to a mass analyser where the decomposition products are analysed as they are evolved. This analytical technique is very sensitive and will scan for Mwt's in a predefined range. It can be used to produce a 3D representation of where different molecular weights are evolved at certain temperatures over the course of the analysis.

2.3.3 Equipment used for Thermal Analysis of PLA Polymers.

Differential Scanning Calorimetry was carried out on a Netzsch DSC 204 operating between –30 and 150 ^{o}C using sample amounts of up to 5mg in aluminium pans.

Thermal Gravimetric Analysis was carried using a Netzsch TG 209 operating from 25 ^{o}C to 300 ^{o}C. Samples of up to 5mg were analysed in Alumina crucibles in air.

Thermal Gravimetric Analysis Mass Spectrometry was carried out on a Netzsch STA 449 C operating between 25 ^{o}C and 150 ^{o}C and detecting masses between 0 and 96 amu, under Argon.

2.4 Techniques for the Determination of Surface Tension

There are several commonly used techniques for the determination of surface tension.

There are methods that measure the surface tension directly and can be used as a means of acquiring the CMC values for solutions and there are methods that can provide more information on wettability and give more information on what is actually happening at the surface or interface and can be used indirectly to acquire values for surface tension.

2.4.1 Tensiometers as a Method of Acquiring Surface Tension

The two most commonly used types of tensiometer are the Du Nouy ring and the Wilhelmy plate methods. Both are capable of directly measuring the force applied at the point where the ring or plate breaks from the surface of the liquid. For the purposes of this thesis only the Wilhelmy plate method will be described in any detail.

The Wilhelmy plate method requires a plate of known dimensions (paper or platinum are commonly used) suspended from a microbalance that is capable of measuring the force applied to the plate by a surface. When the plate is suspended at the gas-liquid interface (see Figure 2.4.1) there are several forces that act upon it and are taken into account.

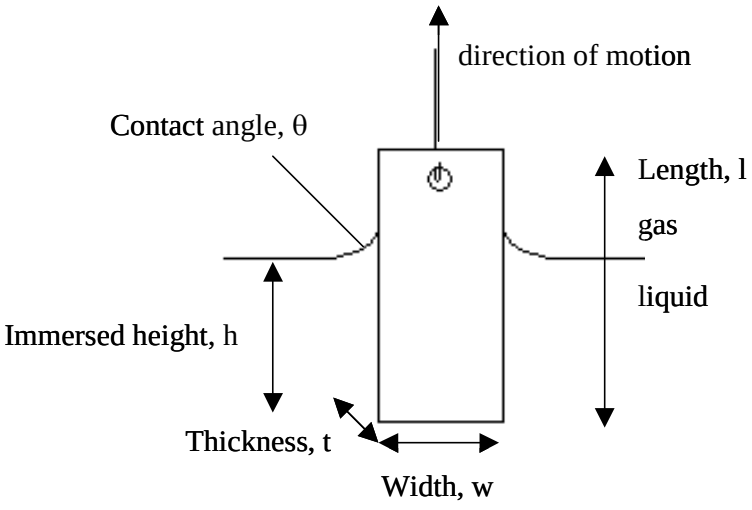


Figure 2.4.1 Wilhelmy plate suspended at the liquid-gas interface

The forces acting on the plate consist of: the weight of the plate, the upthrust on the submerged part of the plate and the surface tension of the liquid acting on the plate. Knowing the dimensions of the plate and the depth to which it is submerged, then the forces acting on the plate can be expressed as:

$$\text{Force} = (\rho_P V_P)g - (\rho_L V_S)g + 2(w+t)ST\cos\theta \qquad (5)$$

(Force = weight – upthrust + surface tension)

where ρ_P is the density of the plate, V_P is the volume of the plate (l.w.t), ρ_L is the density of the liquid, V_S is the volume of the plate submerged (h.w.t), g is the acceleration due to gravity, θ is the contact angle and ST is the surface tension.

The equation is simplified by zeroing the control unit prior to the experiment so that weight is no longer a factor;

$$\text{Force} = (\rho_L V_S)g + 2(w+t)ST\cos\theta \qquad (6)$$

As the plate is drawn from the liquid the point at which the surface tension is taken is the force when the lower edge finally breaks from contact with the water surface. This simplifies the equation further as the upthrust can now be removed.

$$\text{Force} = 2(w+t)ST\cos\theta \qquad (7)$$

The equation is further simplified, as the lower edge is the point in contact with the surface then the contact angle can be taken as 0^o, so the equation becomes:

$$\text{Force} = 2(w+t)ST \qquad (8)$$

Rearranging the equation for surface tension (ST) is:

$$ST = \text{Force}/2(w+t) \qquad (9)$$

Surface tension is given in units of mN/m.

For aqueous systems, paper plates are used to ensure that a zero contact angle is always in effect, since water can completely adsorb into the paper. Great care must be taken in contact angle measurements, as there are many things that can affect the accuracy. Surface tension is sensitive to temperature and care should be taken to make sure this is kept constant (± 0.5 ^{o}C). Paper plates should never by handled as moisture and grease from the hands can effect measurements and care should be taken to make sure there is no dust on the liquid surface.

2.4.2 Travelling Angle Goniometer for the Determination of Contact Angle

A travelling angle goniometer is a sensitive and accurate method of measuring the contact angle of a liquid on a solid surface. The method this employs is called the drop shape or sessile drop method. Contact angle determination is generally used to look at the wettability of solid surfaces – for instance the hydrophobicity or hydrophilicity of a monolayer on a gold surface.

The instrument consists of an adjustable platform beneath a mounted, adjustable microsyringe from which a drop of the solution may be gently and evenly applied to a surface. The drop is observed through a microscope with an angle adjustment in the eyepiece. To take a measurement the platform is moved so the bottom of the drop and one edge of the drop are in line with the eyepiece and the angle is adjusted to be in line with the slope of the edges of the drop (as seen if Figure 2.4.2). Care must be taken in the measurements, as any dirt on the surface will affect the accuracy of the contact angle.

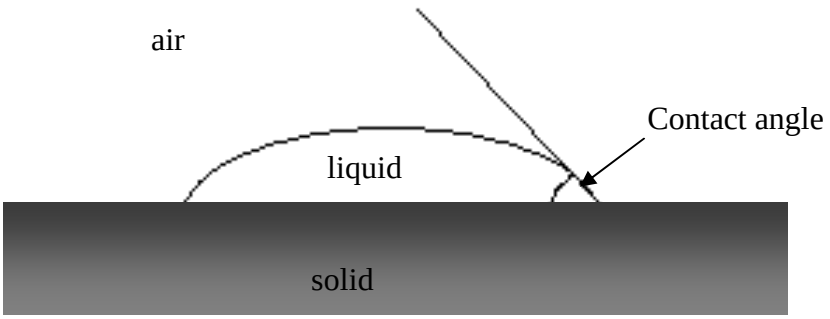


Figure 2.4.2 Shows the contact angle of a drop at the liquid/solid/air interface.

The contact angle of the liquid is related to the critical surface tension of the liquid on the solid. This is however, not a generally useful method of measuring the surface tension of a liquid, as there are many variables and forces to be taken into consideration. These include the work of adhesion, the work of cohesion, work of spreading and wetting tension. The surface tension of a surfactant solution on a surface can only be worked out in relation to a known surface tension on the same surface. Any changes to the surface can lead to dramatic differences in the surface tension. The relationship between contact angle and surface tension is given by Young's equation:

$$\cos\theta = \frac{\sigma_S - \sigma_{LS}}{\sigma_L} \qquad (10)$$

Where σ_L is the surface tension of the liquid; σ_S is the surface free energy of the solid and σ_{LS} is the interfacial tension between liquid and solid.

For the contact angle measurements taken within the work to be discussed, they are all given in reference to water on a clean glass surface. Any change in contact angle between the water and the surfactant solution then illustrates a change in the surface free energy and surface tension – where a decrease in contact angle (i.e drop spreading) relates to a decrease in surface tension between the surface and the liquid. Here, it is not used as a method of determining surface tension of a liquid as the interfacial tension between the solid and liquid is not the same as for water and the solid, therefore that is a variable that cannot be determined without further measurement.

2.4.3 Equipment used for Surfactant Testing

Surface tension measurements were carried out using a Nima ST9000 manual tensiometer using Wilhelmy plate method using paper plates.

Contact angle was measured using a KSV contact angle goniometer, with scope attachment.

2.5 Conclusion

The aforementioned analytic techniques have been employed to some degree throughout the work to be discussed in the following chapters. The actual experimental conditions as well as the actual instruments will be referenced during the appropriate sections, as different equipment has been used in some cases at different times of the research.

It should be noted that some of the equipment is not available at St Andrews and some of the data measurement was carried out in other labs such as Uniqema Wilton (GPC) and University of Nottingham (GPC, DLS, and Emulsion Testing.)

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(b) www.en.wikipedia.org/wiki/Gel_permeation_chromatography

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Chapter 3:
A study of poly(lactic acid) chain length, for Hydrophobicity using the traditional surfactant template.

3.0 Aim

The aim of this chapter was to study the hydrophilic nature of short polyester chains initiated by alcohols (C_6 – C_{20}), diols (C_4 and C_6) and hydroxy-fatty acids. This work is based upon an idea proposed by Uniqema for what was to be an M. Phil project. Within the project several questions had to be answered:

1) What methods were employed for analysis for PLA polymer chains?
2) What was the optimum chain length for poly(lactic acid) hydrophilicity?
3) What was the optimum alkyl chain length in terms of surfactant behaviour?
4) What types of polymer architecture with PLA as hydrophile were possible to still produce surfactant behaviour?
5) Can these polymers be produced within a green context?
6) To investigate the methods that were available to best investigate the surfactant behaviour

The interest was in looking at poly(lactic acid) as a hydrophilic section within a copolymer. In order to ascertain this a variation in ratios of lactide to initiator were used and long chain alcohols were originally employed as the initiators. Several catalysts were chosen, due to their high activity and their requirement of an alcohol initiator, most notably stannous octanoate ($Sn(oct)_2$) and 4-dimethylaminopyridine (DMAP).

The catalytic ring opening polymerisation of lactide using long chain alcohols and hydroxycarboxylic acids as initiators were carried out under various conditions by altering the parameters of temperature, substrate/initiator ratio, catalyst and solvent. The experimental results are given in tables, the maximum chain lengths are taken as the largest peak visible between 5% and 10% intensity where magnification has not been used.

3.1 Starting Materials

Long chain alcohol initiators: Dodecanol was purchased from Aldrich; Heptanol, Octanol, Nonanol and Decanol were purchased from Avocado and used as received. Stannous octanoate was purchased from Sigma and used as it was. 1,4-Butanediol and 1,6-hexanediol were purchased from Fisher Chemical and also used as received.

3,6-Dimethyl-1,4-Dioxane-2,5-Dione (D,L-lactide) and (3S)-cis-3,6-Dimethyl-1,4-Dioxane-2,5-Dione (L-lactide) were purchased from Aldrich and stored < 0 ^{o}C when not in use. Lactide was dried by sublimation in a round bottom flask at 115 ^{o}C under reduced pressure for 2-4 hours prior to use.

All NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer in $CDCl_3$ at 75 MHz for ^{13}C NMR and 300 MHz for ^{1}H NMR – no internal standard was used.

3.2 Uncatalysed Reaction

The uncatalysed reaction occurs in the instance where water is sufficiently present to push the lactide equilibrium across to lactoyl lactate – though small amounts of lactic acid/lactoyl lactate are present as impurities. These lactoyl lactate units are then able to act as nucleophiles for the ROP of lactide; the process is overall slower than when a catalyst is used and high temperatures are required.

Into a clean dry round bottom flask fitted with a water condenser and equipped with a magnetic stirrer, lactide (90 mmoles, 12.97 g) and dodecanol (30 mmoles, 5.59 g) in ratio 3:1 were added and heated to 150 ^{o}C for 72 hours. The final product was an amber viscous liquid, which was then characterised by ^{13}C NMR spectroscopy (see figure 5.1), ESMS and GPC.

Gh17-10: ^{13}C NMR $CDCl_3$ (ppm): 14.09(CH_3, C-1), 16.62-16.88(CH_3, C-18,15), 20.44(CH_3, C-21), 22.66(CH_2 C-2), 25.71(CH_2, C-10), 28.43 - 29.60(CH_2, C-4-

9&11), 31.89(CH_2, C-3), 65.71-65.94(CH_2O, C-12), 66.71(**C**H(CH_3)O, C-20), 68.89-69.43(**C**H(CH_3)O, C-14,17), 169.53-169.69(C=O, C-16,19), 170.18(C=O, C-13). Several residual peaks are also present in the ^{13}C NMR spectrum, 15.76(CH_3, lactide), 26.75(CH_2), 70.06 and 70.39(**C**H(CH_3)O) 72.46(**C**H(CH_3)O, lactide), 173.67(COOH, lactoyl lactate), 175.12(COOH).

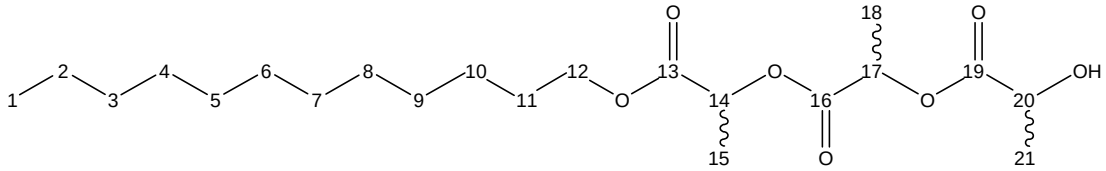


Figure 3.2 Shows a simplified structure showing numbered Carbon units for estimated correlation to ^{13}C NMR shifts of dodecanyl polylactate.

ESMS: Average Mwt (+Na) approx 641.3 Daltons (7 lactate units) 72 amu separation. GPC gives M_n = 581 Daltons, M_w = 730 Daltons, PDI = 1.25.

3.3 Base catalysed ROP

As discussed in Chapter 1, bases are very good transesterification catalysts as they promote the nucleophilicity of the alcohol end groups [1]. In terms of PLA for surfactant applications it was worth looking at these methods as any PLA produced should be a sodium salt – thus enhancing hydrophilic nature of the PLA.

3.3.1 Potassium Hydroxide Catalysed Process

Into a clean dry round bottom flask fitted with a water condenser and equipped with a magnetic stirrer, lactide (90 mmoles, 12.97 g and 30 mmoles, 4.32 g) and initiator dodecanol (30 mmoles, 5.59g), lauric acid (10 mmoles, 2.00 g) and 12-hydroxystearic acid (10 mmoles, 3.00g and 3 mmoles, 0.90 g) were added in ratios of 3:1 and 10:1 (gh17-68d). The reaction mixture was heated to 150 ^oC and potassium hydroxide (5 mmoles) was added. The reaction was run for 24 hours and on cooling a viscous brown tarry liquid formed in the case of dodecanol whilst a brown amorphous solid (wax) formed when lauric acid was the initiator. The samples were

characterised by ^{13}C NMR spectroscopy, ESMS and MALDI-TOF. A summary of the results are shown in Table 3.3.1.

Table 3.3.1 Results of Potassium Hydroxide Polymerisation.

Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (hours)	Ave. Chain Length	Max.[#] Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)	PDI (by GPC)
Gh17-01	30	10[a]	24	~ 7	~ 13	729	1161	1.218
Gh17-25	30	10[b]	24	~ 5	~ 13	561	1137	
Gh17-68a	30	10[b]	1	~ 16	~ 32	1353	2506	
Gh17-68c	30	10[c]	0.5	~ 4	8	611	899	
Gh17-68d	30	3[c]	0.5	~ 12	24	1203	2069	

[#] Maximum for ESMS taken as final peak ~ 10 % intensity; [a] Dodecanol; [b] Lauric Acid; [c] 12-Hydroxystearic acid.

Gh17-01 (Dodecanol : L-Lactide 3:1) ^{13}C NMR $CDCl_3$ (ppm): 14.51(CH_3, C-1), 17.06 - 17.23(CH_3, C-15,18), 20.42-20.87(CH_3, C-21), 23.07(CH_2, C-2), 26.12(CH_2, C-10), 28.83 - 30.01(CH_2, C-4-9&11), 32.29(CH_2, C-3), 66.11 & 66.23(CH_2O, C-12), 67.11(**C**H(CH_3)O, C-20), 69.43 – 69.81(CH(CH_3)O, C-14,17), 169.66(C=O, C-16,19) and 170.59(C=O, C-13).

ESMS: Average Mwt (+Na, +K) ~ 729 Daltons (7 lactate units) 72 amu separation.

GPC: Mwt = 730, Mn = 550, Mw = 670, PDI = 1.218

Gh17-25 (Lauric Acid : *rac*-Lactide) ^{13}C NMR $CDCl_3$ (see Figure 3.3.1a) (ppm): 14.51(CH_3, C-1), 16.18(CH_3, C-20), 17.03(CH_3, C-14,17), 20.74(CH_3, C-?), 23.08(CH_2, C-2), 25.22(CH_2, C-10), 29.53 – 30.01(CH_2, C4-C9), 32.30(CH_2, C-3), 34.58(CH_2, C-11), 66.99(CH(CH_3)OH, C-19), 69.41 – 69.82(CH(CH_3)O, 169.84(C=O, C-15, 18), 174.26(C=O, C-12), 179.08(COO^-, C-21 and unreacted lauric Acid)

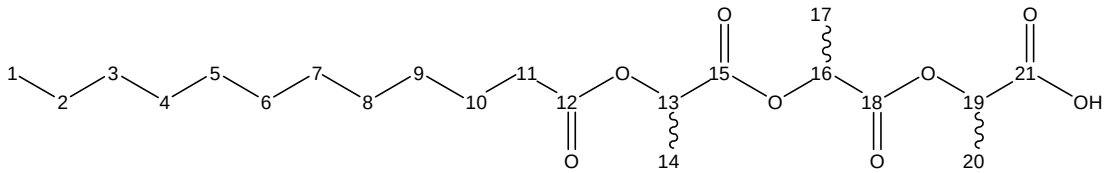


Figure 3.3.1a: Simplified Structure of a Lauric Acid initialised Polymer Showing Numbered Carbon Units for Estimated Correlation to ^{13}C NMR Shifts of gh17-25.

ESMS: Average Mwt (+Na) ~ 561.07 Daltons (5 lactate units) 72 amu separation.

Gh17-68a (Lauric acid : *rac*-Lactide; 1 : 3) ^{13}C NMR $CDCl_3$ (significant peaks) (ppm): 16.21(CH_3, C-20), 17.04(CH_3, C-14,17), 67.09 ($CH(CH_3)O$, C-19), 69.41($CH(CH_3)O$, C-13, 16), 170.04 (C=O, C-15, 18) and 179.48 (COO^-, unreacted lauric acid).
MALDI-TOF: Average Mwt ~ 1353 (16 lactate units) 72 amu separation.

Gh17-68c (12-hydroxystearic acid : *rac*-lactide; 1 : 3) ^{13}C NMR $CDCl_3$ (see Figure 5.2.1) ppm: 14.47(CH_3, C-18), 16.20(CH_3, C-21, 24), 17.04 & 17.32 (CH_3, C-21, 24), 20.09(CH_3, C-27), 23.02(CH_2, C-17), 25.09(CH_2, C-14,8), 25.53 & 26.00(CH_2, C-3), 29.37, 29.53, 29.62, 29.70, 29.77, 30.01 & 30.09 (CH_2, C-4-9 & 15), 32.24(CH_2, C-16), 34.4(CH2, C-11,13), 37.76 & 37.81(CH_2, C-2), 67.1(**C**H(CH_3)O, C-26), 69.43, 69.6 & 69.85($CH(CH_3)O$, C-20, 23), 72.52 & 72.87(unreacted lactide), 76.87(CH-O, C-12), 169.81(C=O, C-22, 25), 170.03(C=O, C-19) and 179.30(COOH, C-1).
ESMS: Average Mwt ~ 611 Daltons (4 lactate units) 72 amu separation.

Gh17-68d (12-hydroxystearic acid : *rac*-lactide; 1 : 10) ^{13}C NMR $CDCl_3$ (significant peaks) ppm: 67.08(**C**H(CH_3)O, C-26), 69.41 & 69.59(**C**H(CH_3)O), 169.79(C=O, C-22,25) and 170.04(C=O, C-19).
MALDI-TOF: Average Mwt ~ 1203 (12 lactate units)

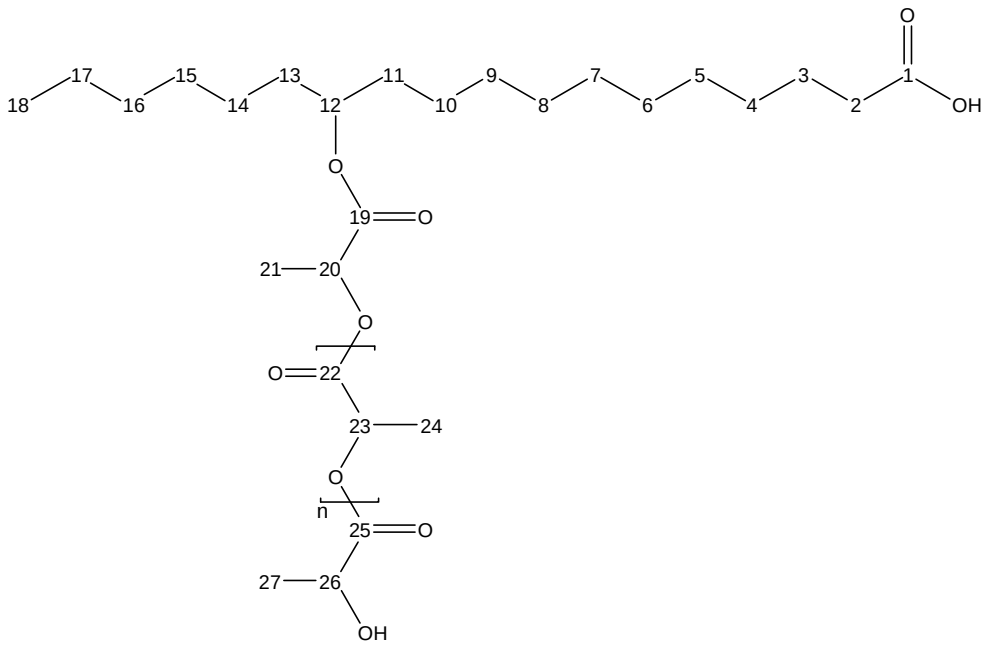


Figure 3.3.1b. Simplified Structure of a 12-Hydroxystearic Acid initialised Polymer Showing Numbered Carbon Units for Estimated Correlation to ^{13}C NMR Shifts.

3.3.2 Potassium Carbonate Catalysed Process

Into a clean dry three-necked flask rac-lactide (30 mmoles, 4.32 g) and the alcohol initiator dodecanol (10 mmoles, 1.86 g), lauric acid (10 mmoles, 2.00 g) and heptanol (10 mmoles, 1.16 g) were added in controlled ratios and heated to 130 ^{o}C. When melting was complete potassium carbonate (5 mol %) was added directly to the melt and reaction allowed to proceed from between 10 and 90 minutes. The resulting polymer was then analysed by ^{13}C NMR and ESMS or Maldi-TOF for Mwt exceeding ~ 1500 Daltons. The results are summarised in Table 3.3.2.

Table 3.3.2 Results of potassium carbonate catalysed polymers.

Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (minutes)	Ave. Chain Length	Max. Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)	PDI (by GPC)
Gh17-67	30	10[a]	90	6	10	641	945	
Gh17-68b	30	10[b]	300	~ 10+	~ 24	>921	1968	
Gh17-83	30	5[d]	15	~8	> 24	875	>1883	

[a] dodecanol; [b] lauric acid; [d] heptanol;

Gh17-67: ^{13}C NMR $CDCl_3$ (important characteristic peaks) (ppm): 67.00 & 67.05 (CH(CH3)OH, C-20), 69.40 – 69.75 ($CH(CH_3)O$, C-14,17), 169.75 & 170(C=O, C-16,19), 170.56 & 170.66 (C=O, C-13), 175.53 (COO^-, ?).

Gh17-68b: ^{13}C NMR $CDCl_3$ (important characteristic peaks) (ppm): 69.41 & 69.59 ($CH(CH_3)O$, C-13,16), 170.10 & 170.7(C=O, C-15,18) and 180.26 (COO^-, C-21, unreacted lauric acid).

Gh17-83: ^{13}C NMR $CDCl_3$ ppm: 14.05 (CH_3, C-1), 15.81 (CH_3, lactide), 16.64, 16.74 & 16.83 (CH_3, C-10, 13), 20.51(CH_3, C-16), 22.54(CH_2, C-2), 25.68(CH_2, C-5), 28.45(CH_2, C-6), 28.82(CH_2, C-4), 31.67(CH_2, C-3), 65.71(CH_2O, C-7), 66.71(**C**H(CH_3)O, C-15), 69.04, 69.33 & 69.45(**C**H(CH_3)O, C-9, 12), 72.47(lactide), 169.62(C=O, C-11, 14), 170.18(C=O, C-8).
Maldi-TOF: Average Mwt ~ 875 Daltons (8 lactate units).

3.4 Tin (II) Octanoate Catalysed ROP

The choice of Tin (II) Octanoate as a catalyst for the ROP of lactide was based upon these criteria:

1) Relatively non-toxic
2) Cheap
3) Requires an alcohol initiator to carry out ROP
4) Vast amount is known about its catalytic mechanism

As discussed in chapter 1 its wide use in industrial applications make it an ideal candidate as a catalyst for these particular systems [2,3,4(a,b),5,6].

3.4.1 Poly(lactic acid) Catalysed by $Sn(oct)_2$ in a Melt Polymerisation

Into a clean dry three necked flask equipped with condenser and magnetic stirrer, lactide and initiator was added in controlled ratios. These mixtures were heated to 150 ^{o}C and to the melt stannous octanoate was added (0.15 mls) via a syringe. The reactions were allowed to proceed for 6 hours and the final products were characterised by ^{13}C NMR spectroscopy (for assignments see Appendix A), ESMS, MALDI-TOF mass spectrometry and GPC. See Tables 3.4.1 for summary of reaction conditions.

Table 3.4.1 Results of Stannous Octanoate Melt Polymerisations

Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (hours)	Ave. Chain Length	Max. Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)	PDI (by GPC)
Gh17-03	90	30[a]	6	6	11	641	1001.42	1.4
Gh17-06	50	25[a]	5	5	9	569	857	-
Gh17-08	60	20[f]	6	6	11	585	945	-
Gh17-13	100	50[f]	5	1	3	225.1	369	1.071
Gh17-24a	50	1	6	6	12	527	959	-
Gh17-24b	50	1	6[t]	6	12	527	959	-
Gh17-33a	90	30	3	6	12	613	1045	-
Gh17-33b	90	30	6	5 – 7	12	613	1045	-

[a] dodecanol; [f] octanol; [t] @ 115 ^{o}C.

3.4.2 My own observations

Into a clean dry three necked flask equipped with condenser and magnetic stirrer, lactide and initiator were added in controlled ratios. The reactants were heated to 135^{o}C and when a melt was achieved stannous octanoate (5 mol%, ~ 8 drops) was added via a Pasteur pipette. During initial tests, samples were taken at regular intervals for ESMS and ^{13}C NMR spectroscopy, at intervals of 5, 10, 20, 40, 60 and 80 minutes. Comparison was drawn between molecular weights and peak separation in the ESMS, NMR spectra was used to observe how much lactide had reacted. Further reactions were carried out from between 10 and 20 minutes with the same catalyst amounts. Products were analysed by ^{13}C NMR spectroscopy (for full assignments Appendix), ESMS and MALDI-TOF mass spectrometry. See Table 3.4.2 for summary of reaction conditions.

Table 3.4.2 Results of Other stannous octanoate initiated polymers

Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (mins)	Ave. Chain Length	Max. Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)
Gh17-76	30[x]	5[d]	4	8	18	487	777
Gh17-77	30	5[g]	10	10	28	887	2184
Gh17-79	30	5[c]	10	10	26	1060	2197
Gh17-82a	30	10[d]	5	6	10	571	859
Gh17-82b	30	10[d]	10	6	10	571	859
Gh17-82c	30	10[d]	20	6	10	571	859
Gh17-82d	30	10[d]	40	6	10	571	859
Gh17-82e	30	10[d]	60	6	10	571	859
Gh17-82f	30	10[d]	80	6	10	571	859
Gh17-86	20	1[d,Ω]	15 + 10	10	58	959	4416
Gh17-87a	30	10[d]	10	6	12	571	1003
Gh17-87b	30	10[d,Ω]	15	6	12	571	1003
Gh17-87c	30	10[d,Ω]	20	6	12	571	1003
Gh17-87d	30	10[d,Ω]	30	8	12	715	1003
Gh17-87e	30	10[d,Ω]	60	6	10	571	859
Gh17-87f	80	10[d,Ω]	80	6	10	571	859
Gh17-88	30	5[d,Ω]	10 + 10	10	40	959	3119
Gh17-89	30	3[c,Ω]	10 + 10	14	40	1447	3321

[c]12-HSA;[d] heptanol; [g] nonanol; [Ω] end capped with succinic anhydride; [x] glycolide.

3.5 Lewis Base Catalysed ROP

DMAP [7] is a very common nucleophilic organic catalyst for a wide variety of applications in organic chemistry. It is also a very potent transesterification catalyst ideal for use in lactide polymerisation. Like other methods this one also must employ an alcohol initiator, and only works with primary and secondary alcohols. DMAP however is more toxic than the tin catalyst and more catalyst is required to carry out the reactions. However, it works very well as a catalyst at high T and at a lower temperature in a suitable solvent and can be used in some solvent systems where $Sn(oct)_2$ is unsuitable.

3.5.1 Solvent based system

Into a clean dry three necked flask equipped with condenser and magnetic stirrer, lactide and initiator: Dodecanol was added in ratios 3:1, 6:1, 10:1, 20:1, 50:1 and 100:1; 12-hydroxydodecanoic acid 3:1; and 1,4-butanediol 6:1 and these were dissolved in dichloromethane (50 mls) and heated to 35 ^{o}C. When the reactants had dissolved 4-dimethylaminopyridine (DMAP) was added (5 mmoles) and the reactions proceeded for 6 hours, or 24 hours in the case of 1,4-butanediol. For summary of results see Table 3.5.1.

Table 3.5.1 DMAP catalysed Reactions in DCM @ 35 ^{o}C

Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (hours)	Ave. Chain Length	Max. Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)	PDI (by GPC)
Gh17-14	60	20[a]	24	6	12	641	1073	1.33
Gh17-15	30	10[b]	24	6	10	671	959	
Gh17-16	60	10[a]	24	8 – 10	14	>785	1217	
Gh17-17	100	10[a]	24	12	18	1073	1505	
Gh17-18	100	5[a]	24	12	18	1073	1505	
Gh17-21	50	1[a]	24					
Gh17-23	100	1[a]	24	8	20	761	1625	
Gh17-27	60	10[j]	24	7 - 8	15	>617	1193	

[a] dodecanol; [b] lauric acid; [j] 1,4-butanediol;

3.5.2 Melt polymerisation

Into a clean dry three necked flask equipped with condenser and magnetic stirrer, lactide and alcohol initiator in controlled ratios (ratios for co-polymerisation with LP1 were approximated from the mass spectra of LP1) were added and heated to 130 ^{o}C. To the melt DMAP (5 mmoles) was added and the reactions allowed to proceed for varied times. The products were characterised by ^{13}C NMR spectroscopy, ESMS and MALDI-TOF mass spectrometry. A summary of the experimental results are given in Table 3.5.2.

Table 3.5.2 Results of DMAP melt polymerisations.

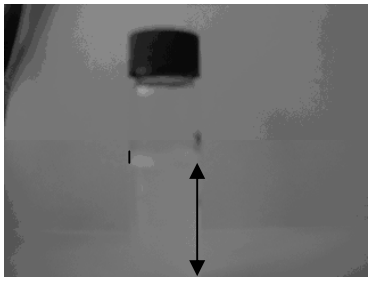
Experiment Name	Conc. of Lactide (mmoles)	Conc. of Initiator (mmoles)	Reaction Time (hours)	Ave. Chain Length	Max. Chain Length	Ave. Mwt (Daltons)	Max. Mwt (Daltons)
Gh17-28	50	1[a]	36	_	_	_	_
Gh17-30	90	30[j]	36	4	10	401	833
Gh17-31a	90	30[a]	6	3	9	425	857
Gh17-31b	90	30[a]	12	4 - 5	10	> 401	833
Gh17-31c	90	30[a]	18	3	8	425	785
Gh17-32a	20	1[a]	3	6	38	641	2946
Gh17-32b	20	1[a]	6	6	35	641	2442
Gh17-35	90	30[g]	4	5	10	527	887
Gh17-37	60	20[d]	5	9	9	499	787
Gh17-38	60	20[k]	6	3 – 5	9	553	913
Gh17-39	60	20[l]	6	5	11	653	1085
Gh17-40	60	20[m]	6	5	11	681	1113
Gh17-41	50	5[k]	6	7	40	779	3145
Gh17-43	60	20[n]	3	6	9	573	789
Gh17-44	60	10[o]	3	4	12	599	1171
Gh17-45	30	10[b,d]	4	4	9	497	857
Gh17-50	30[x]	10[a]	0.75	3	7	383	615

[a] dodecanol; [b] lauric acid; [d] heptanol; [g] nonanol; [j] 1,4-butanediol; [k] hexadecanol; [l] octadecanol; [m] eicosanol; [n] 1,6-hexanediol; [o] 1,12-octadecanediol; [x] glycolide instead of lactide.

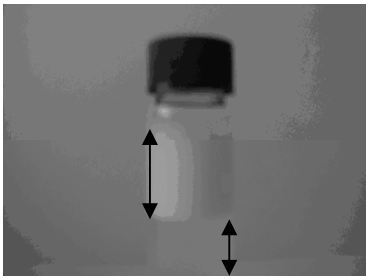
3.6 Surfactant Tests

3.6.1 Foaming

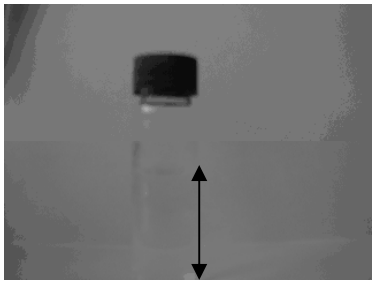
Into a clean test-tube polymer (0.1g) was added. To this distilled water (10 ml) was added and the test tube shaken rigorously for 1 minute. The amount of foaming was observed as was the amount of polymer dissolved. The solution was shaken for a further two minutes. If foaming and or solubility had not improved, 3 drops of sodium hydroxide solution (1 M) was added and the tube shaken again (increases pH to ~ 10.) Since quantifying these results are somewhat difficult without being able to measure CMC or Surface Tension, results of foaming tests were graded on a 5 point scale, from 1 showing no surfactant behaviour to 5 showing ideal characteristics. The results are shown in Table 3.6.1, the pictures below illustrate the differences in solubility of the polymers and help to scale the results in the table.



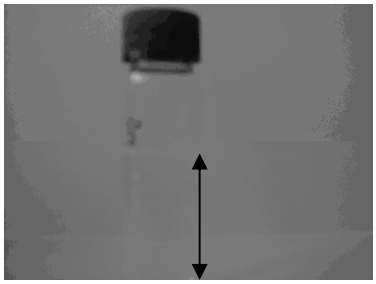
Gh17-43(4)



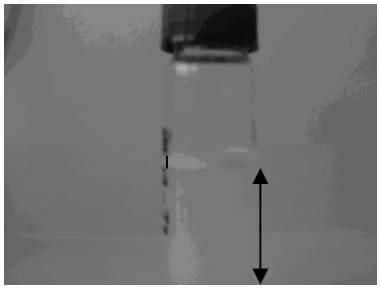
Gh17-43 + 3 drops of base (5)



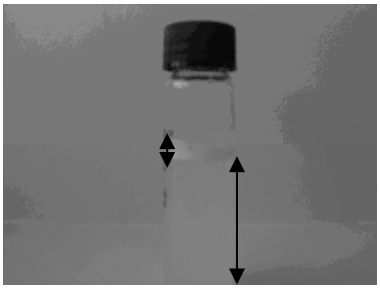
Gh17-72c (1)



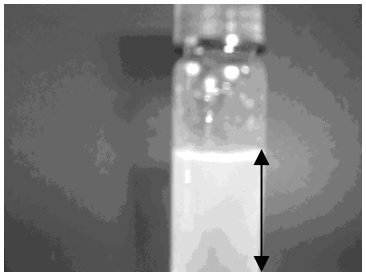
Gh17-72c + 3 drops of base (1)



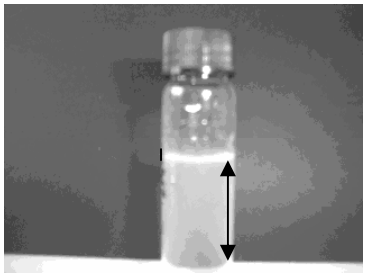
Gh17-71 (4)



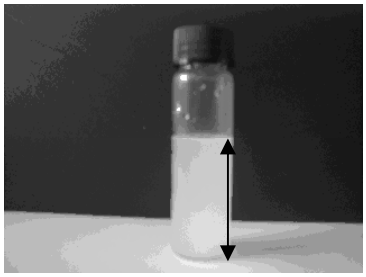
Gh17-71 + 3 drops of base (4)



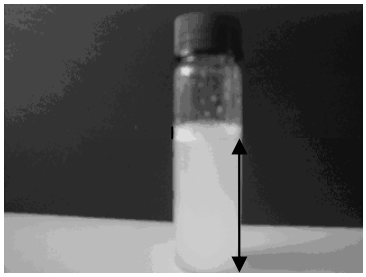
Gh17-43(2)



Gh17-43 + 3 drops base (3)



Gh17-67 (2)



Gh17-67 + 3 drops of base (4)

Pictures Above illustrate the Foaming and how these compare to the scale. The arrows on the right hand side illustrate the depth of solution. The line on the left hand side illustrates the amount of foaming if any.

Table 3.6.1a. Results of Foaming Tests.

Experiment Number	Initiator	Initial Foaming	Foaming on addition of base	Residue Present
Gh17-01	Dodecanol	3	4	Yes (brown oil)
Gh17-02	Dodecanol	3	3	Yes
Gh17-03	Dodecanol	3	4	Yes
Gh17-35	Nonanol	4	4	Yes
Gh17-37	Heptanol	4	5	Yes (oil)
Gh17-38	Hexadecanol	2	2	Yes (oil)
Gh17-39	Octadecanol	1	1	Yes
Gh17-40	Eicosanol	2	2	Yes
Gh17-41	Hexadecanol	1	1	Yes
Gh17-43	1,6-Hexanediol	2	2	Yes
Gh17-44	1,12-octadecanediol	4	4	Yes
Gh17-45	Dodecanol/lauric acid	5	5	No

Scale: 1- Insoluble no surfactant behaviour; 2- Soluble, but no surfactant behaviour; 3- Some foaming, but with insoluble residue; 4- Foaming, with little residue and 5- Soluble and foaming.
* Goes clear on addition of base.

Table 3.6.1b Results of Foaming Tests.

Experiment Number	Initiator	Initial Foaming	Foaming on addition of base	Residue Present
Gh17-47	Dodecanol/ 1,10-decanedicarboxylic acid	3	4	Yes
Gh17-48	1,6-hexanediol/ 1,10-decanedicarboxylic acid	2	2	Yes
Gh17-49	Dodecanol/lauric acid	4	4	Yes
Gh17-50*	dodecanol	3	4	Yes
Gh17-53	Heptanol/ 1,10-decanedicarboxylic acid	4	5	No
Gh17-65	12-HSA	3	4	Yes
Gh17-66	12-HSA	3	4	Yes
Gh17-67	Dodecanol	2	4	Yes
Gh17-69	12-HSA	3	3	Yes
Gh17-70	12-HSA	3	4	Yes
Gh17-71	12-HSA	4	4	Yes

Table 3.6.1c. Results of Foaming Tests.

Experiment Number	Initiator	Initial Foaming	Foaming on addition of base	Residue Present
Gh17-74f	Heptanol	3	4	Yes
Gh17-76	Heptanol	3	4	Yes
Gh17-77	Nonanol	3	3	Yes
Gh17-78	Nonanol	2	3	Yes
Gh17-80	Heptanol	3	3	Yes
Gh17-81	Heptanol	4	4	Yes
Gh17-82	Heptanol	1	3	No
Gh17-83	Heptanol	1	1	Yes
Gh17-86	Heptanol	3	1	Yes
Gh17-87f	Heptanol	2	5	Yes
Gh17-88	Heptanol/ succinic anhydride	3	4	Yes
Gh17-89	12-HSA/succinic anhydride	1	4	Yes*
Gh17-93f	Heptanol	3	5	Yes

3.6.2 Contact Angle Measurements

From foaming tests several candidates for contact angle measurement were chosen. For this solutions of the better candidates were prepared (0.1g in 100 mls of degassed distilled water). Using a contact angle goniometer equipped with microsyringe and dropping onto a clean glass surface the contact angle was measured. The average contact angle was then taken for these samples are shown in Table 3.6.2

Table 5.6.2: Shows contact angles measured on glass slides

Experiment Number	Average Contact angle (Water)	Average Contact Angle
Gh17-32	26^o	63.17^o
Gh17-45	26^o	8^o
Gh17-49	26^o	11^o
Gh17-89	22.8^o	26.1^o

3.6.3 Infra-Red

Into a clean dry test-tube polymer (~ 0.1 g) was added, along with a stirrer bar. To this distilled water (10 ml) was added and the tube shaken vigorously. To aid in dissolving the test-tubes were immersed in a sonic bath for 20 minutes. The polymer solution was then shaken rigorously several times and left to stir for 24 hours. After 24 hours the polymer was recovered, either through filtration, extraction (although the polymer once water is co-ordinated around is insoluble in most solvents) or evaporation. The recovered polymer was then dried *in vacuo* before being weighed.

The IR spectra of the recovered polymer was then run along with the initial product on a Perkin Elmer Spectrum GX FT-IR using KBr discs for solid samples, or neat for liquids/gels. NMR spectrum could not be run on recovered samples due to poor solubility in most common solvents (D_2O, $CDCl_3$, d_6 benzene, d_3-acetonitrile and d_6-acetone).

3.7 Discussion

The poly(lactic acid) long chain alkyl esters and copolymers were produced by ring-opening polymerisation using a variety of previously reported catalytic methods [5,8,11,28,33] and used both solution and melt polymerisation conditions. Typically in a melt polymerisation the lactide and initiator were heated to melting (130 ^{o}C) and the catalyst KOH, K_2CO_3, $Sn(oct)_2$, p-TSA or DMAP was added to begin the reaction. For solution based reactions the lactide and initiator were dissolved in solvent and heated (to 35 ^{o}C for DCM and 70 ^{o}C for toluene) before the addition of catalyst (DMAP, p-TSA or triflic acid). The polymer products were obtained by evaporation of solvent.

For most reactions only the ^{13}C NMR spectra were run, the ^{1}H NMR spectra were difficult to characterise and had poor resolution although this could possibly be improved by running at 500 MHz.

3.7.1 Polymer Architecture

A series of peaks is observed in the mass spectra of the new polymeric materials. Their relative spectrum intensities give some indication of the molecular weight distribution although this is not quantitative as the relative intensities for high molecular weight polymers may be reduced because of their lower volatility.

In many cases the parent ions are observed but sometimes complication can arise from interactions with the matrix or with cations present in the catalyst used. An example of this is when KOH is used as the catalyst. Two series of peaks are obtained, as from the parent ions and from $[M+K]^+$.

In addition to the molecular weight distribution, mass spectra also give information about the course of the reactions and especially the extent to which transesterification (or racemisation of chiral centres) occurs. Racemisation of the lactide rings [8] can occur in the presence of strong base. This occurs due to the acidity of the methine proton ($pK_a \sim 17$), which occurs as a result of its position in the lactide ring lactide. When this proton is lost the anion formed has a has a planar geometry due to the delocalisation of the negative charge and when reprotonation occurs it can attack from either side of the ring leading to racemisation (Figure 3.7.1).

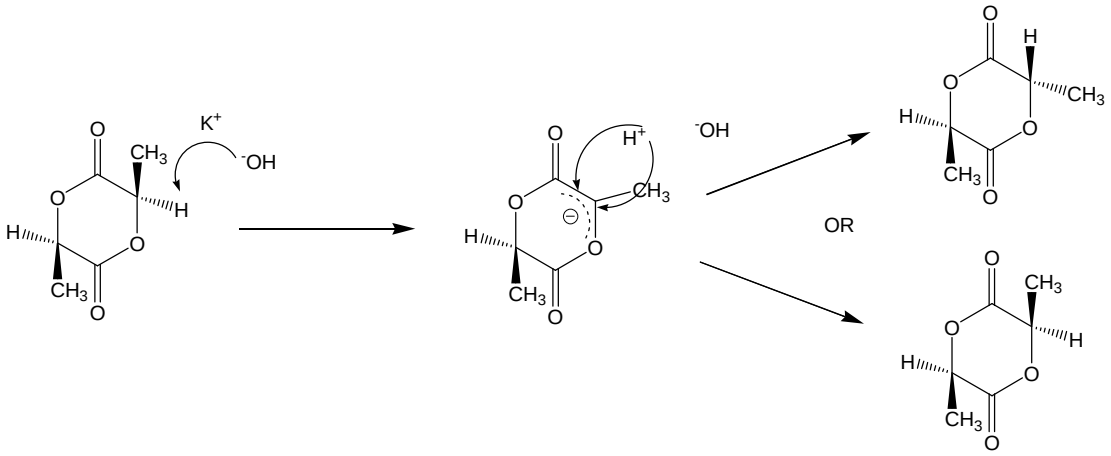
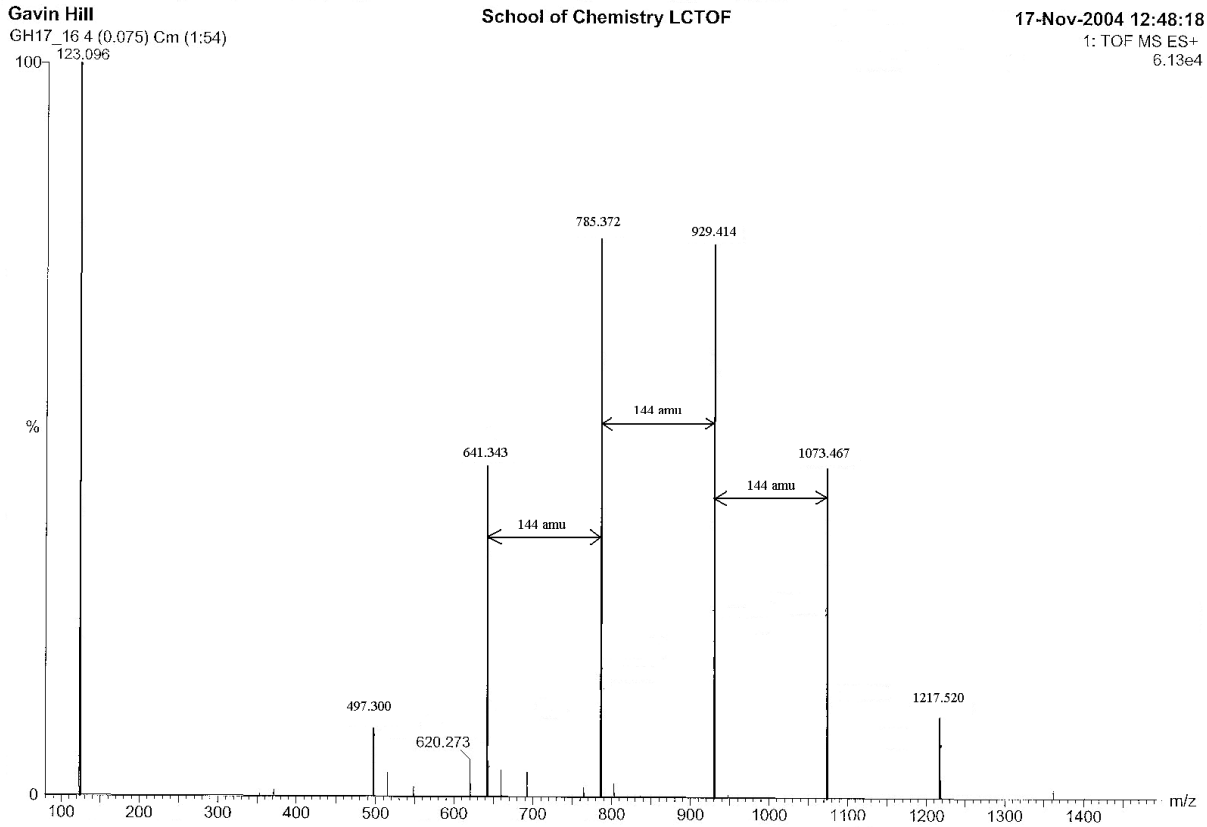


Figure 3.7.1a. Shows the racemisation of lactide rings in the presence of strong base.

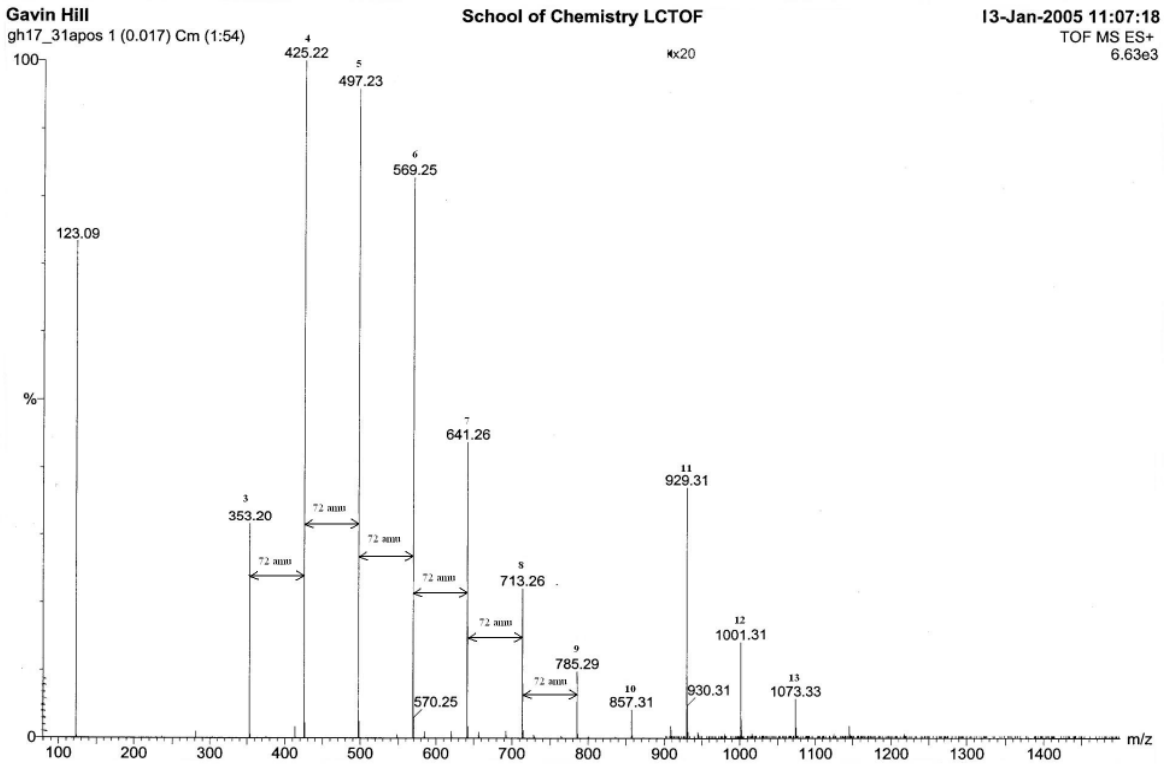
Thus in this manner it is possible to form some *meso*-lactide. This along with transesterification of the polymer chains can lead to truly randomised polymers that could theoretically contain all known tetrad sequences.

The average molecular weight can be compared to what the expected molecular weight of the polymer is determined by the ratio of lactide to initiator. The closer the predicted and experimental values then the more predictable the molecular weight obtained from the polymerisation method is.

Lactide polymerisation should give polymers in which the peaks are separated by 144 amu (lactoyl lactate), as in Spectrum 3.7.1b. which was obtained from a low temperature DMAP solution reaction (gh17-16) with dodecanol as the initiator. However, if transesterification occurs the individual polymers are separated by only 72 amu (lactate). In spectrum 3.7.1c, which was obtained from a polymer produced using identical monomer to initiator ratios and catalyst amounts but was run as a melt at 130 ^{o}C, shows peak separation of 72 amu.



Spectrum 3.7.1b. Mass Spectrum of Gh17-16, a 3:1 *rac*-lactide : dodecanol reaction in DCM @ 35 ^{o}C for 6 hrs.



Spectrum 3.7.1c. Mass Spectrum of Gh17-31, a 3:1 *rac*-lactide : dodecanol reaction @ 135 ^{o}C for 6 hrs.

In the spectra of gh17-01 to gh17-13 it can clearly be seen that the molecular weight separation is 72 mass units (lactate). 72 amu was then used as the standard for 1 monomer unit throughout the lactide polymerisations. It would be expected that under ideal conditions separation would be 144 amu (lactoyl lactate), as this represents 1 ring opened lactide unit.

In the DMAP solution reactions it can clearly be seen that in the mass spectra of gh17-14 to 18 and gh17-21,23 and 27 that the separation here is now 144 mass units (lactoyl lactate) under mild conditions.

3.7.2 Transesterification

Transesterification (Figure 3.7.2) occurs when the secondary alcohol of the terminus reacts at a carbonyl carbon of a neighbouring chain leading to chewing up and chain transfer, this can occur extensively and is unselective with regard to which carbonyl it attacks, but it is a factor that can be controlled through temperature, catalyst and reaction time. In DMAP solution reactions no transesterification occurred, but in protic acid reactions under similar conditions they did. The effect of transesterification was clear from the ESMS, but it was unknown when this effect started.

It became apparent when carrying out reactions with glycolide that the stannous octanoate reactions and DMAP melts occur more rapidly than was initially realised. In the first reaction with glycolide the reaction stopped after 4 mins, due to the formation of high melting point solid ~160 ^{o}C formed. The analysis of the product and this result led to an investigation of how the mass spectra altered over time.

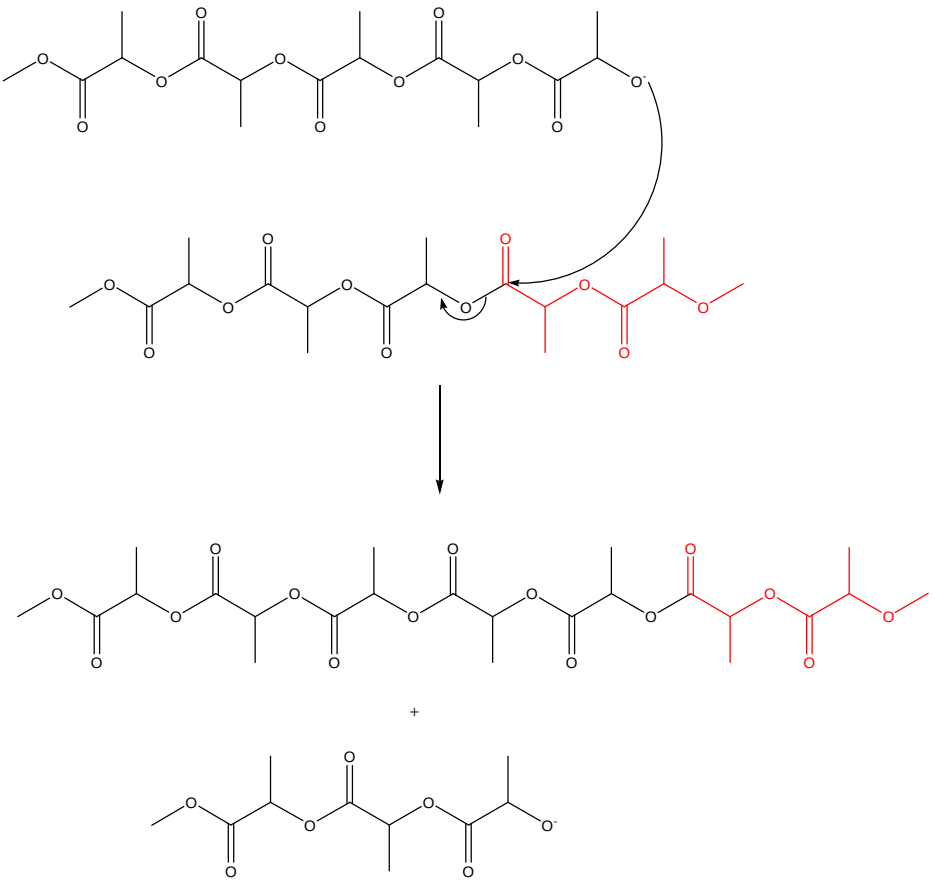
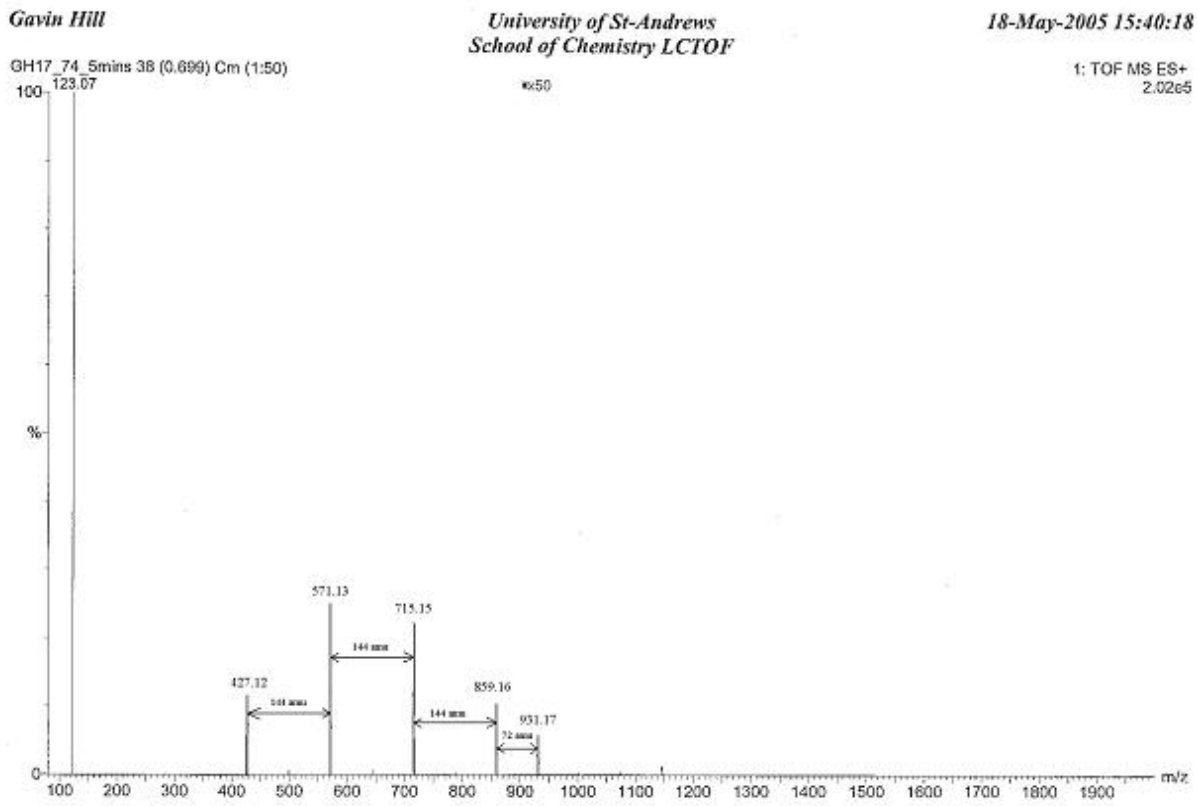
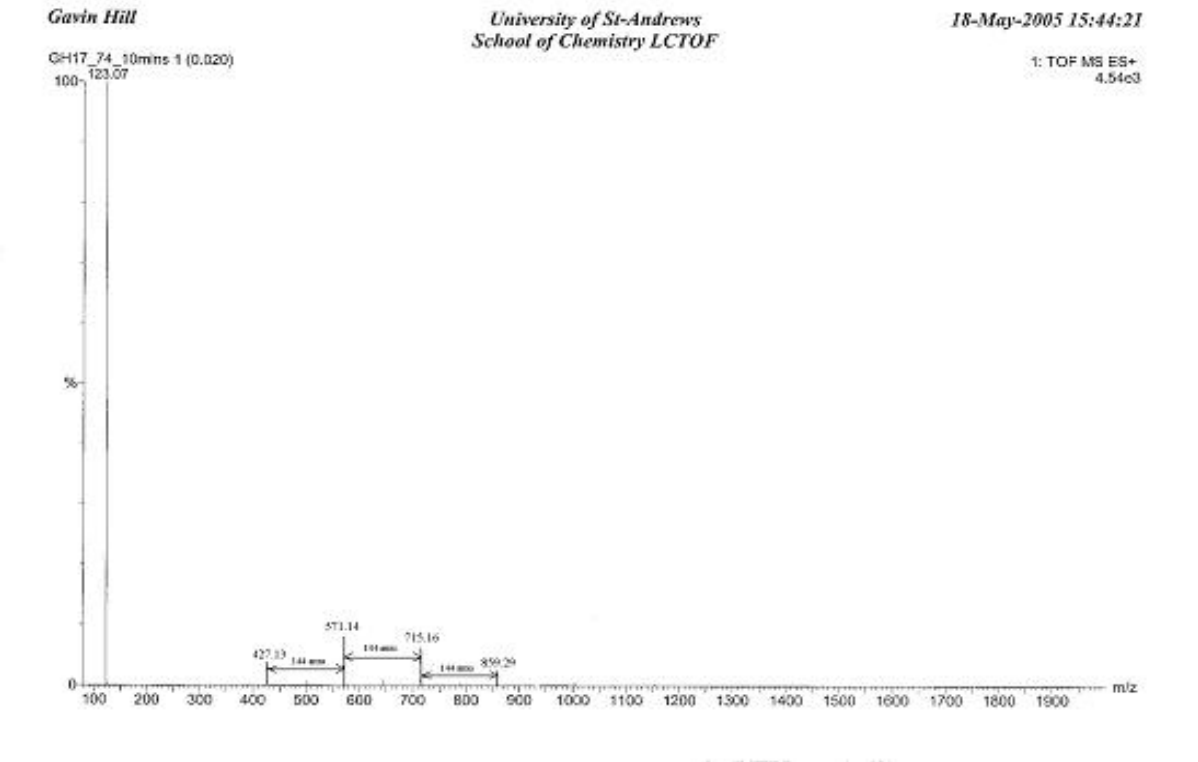


Figure 3.7.2: Mechanism of back-biting (transesterification) reaction.

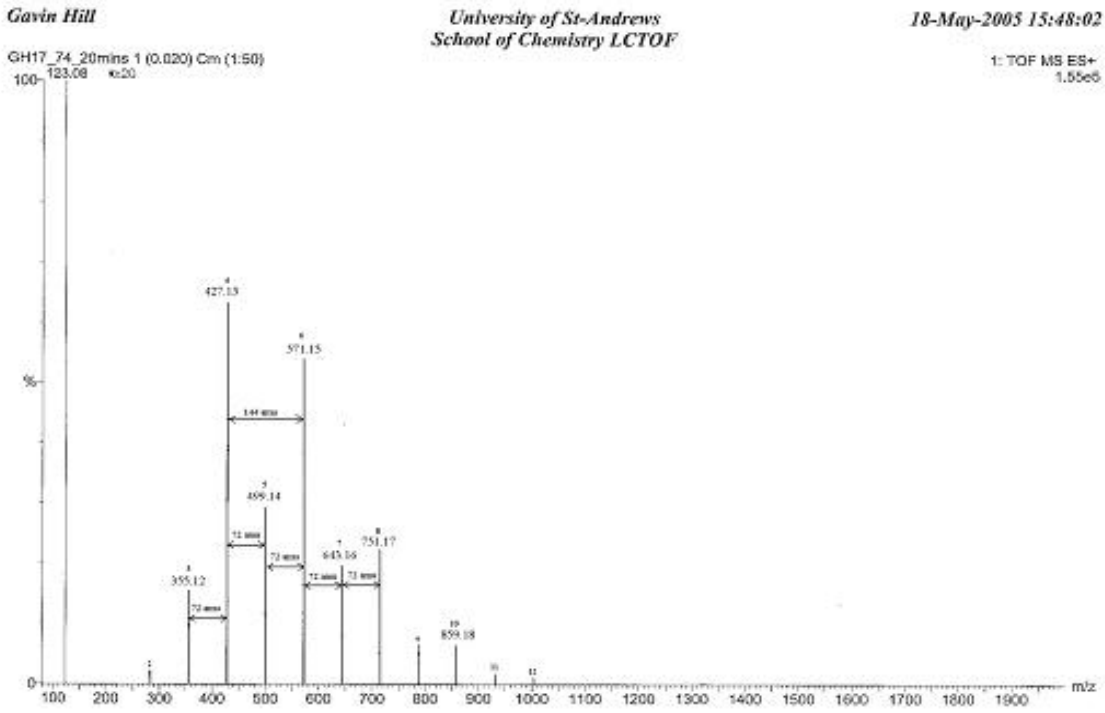
With gh17-74 a 3:1 lactide : heptanol was run in a DMAP melt, with samples taken at regular intervals and analysed by NMR spectroscopy and ESMS. The result (Spectra 6.1.2a-f) showed that initially during the reaction the polymer masses were separated by 144 mass units, but as time went on this altered. After 20 mins an even-odd distribution emerged and the average molecular weight began to shift. After 80 mins the predominant peak is at 5 lactate units and there has been an increase in the lower mass fragments also, with 3 lactate units now far more pronounced. Here, the Gaussian overall shape of the spectrum suggests that transesterification has completely randomised the polymer.



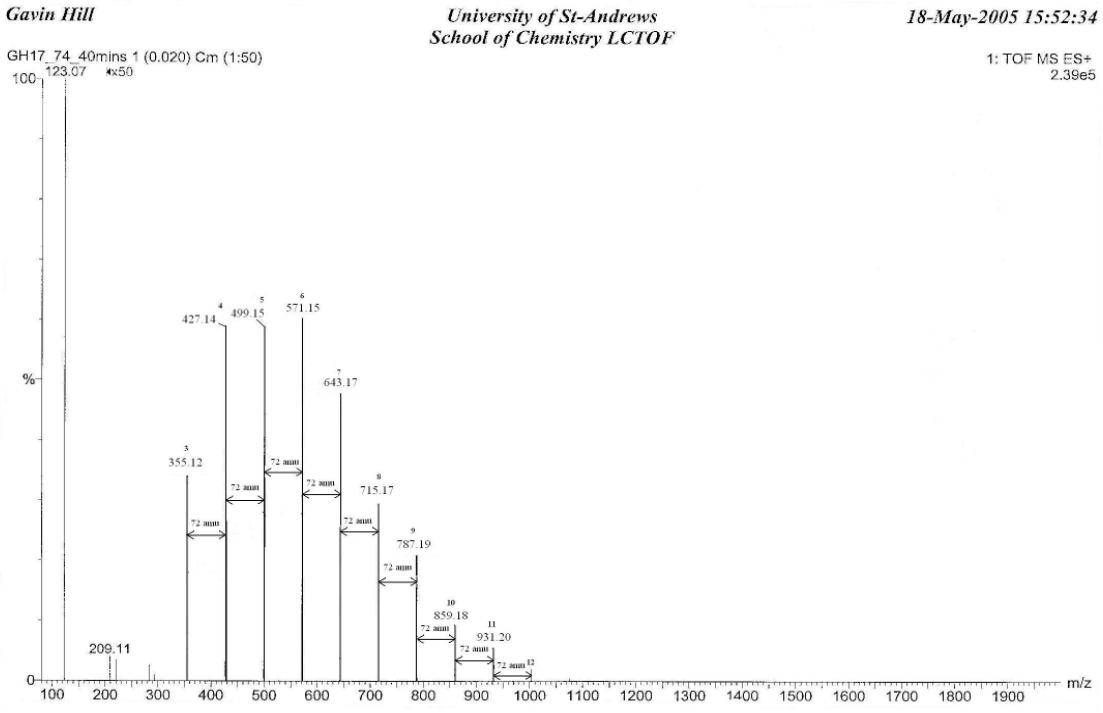
Spectrum 3.7.2a: Gh17-74 after reaction time of 5 mins.



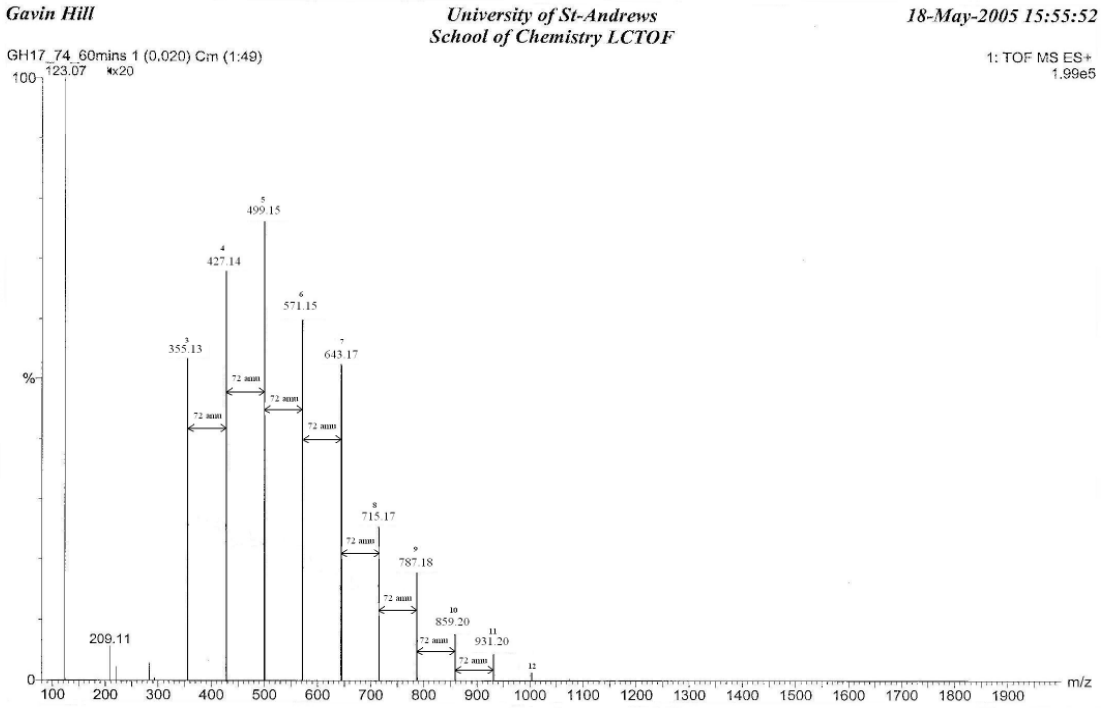
Spectrum 3.7.2b: Gh17-74 after reaction time of 10 mins.



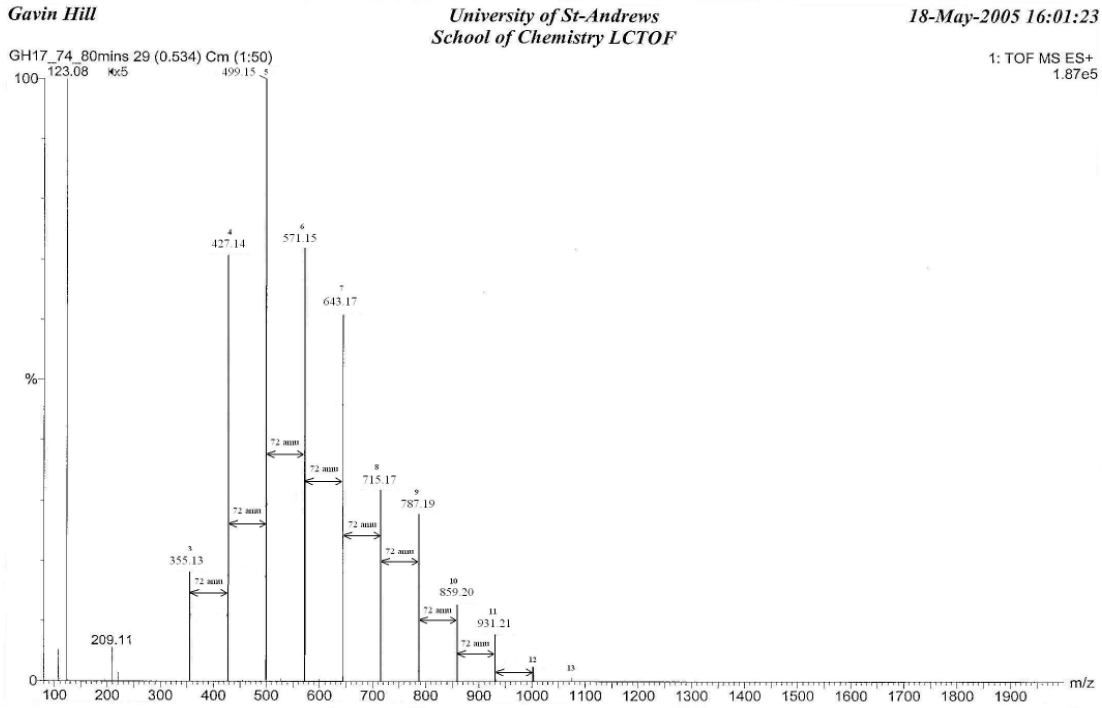
Spectrum 3.7.2c: Gh17-74 after reaction time of 20 mins.



Spectrum 3.7.2e: Gh17-74 after reaction time of 40 mins.



Spectrum 3.7.2e: Gh17-74 after reaction time of 60 mins.



Spectrum 3.7.2f: Gh17-74 after reaction time of 80 mins.

A similar reaction gh17-82 was carried out with stannous octanoate as catalyst and in this instance some transesterifcation was visible from after 5 minutes, but the effect here was interesting in that the average molecular weight did not shift, and even after 80 mins although transesterification had occurred it was not as great as for DMAP, in this case it appears more like two Gaussian's are present, one for odd and one for even numbers of lactate units, in this instance the presence of peaks at 3 lactate and at 11 and 12 lactate units become more prevalent with time.

Another experiment looking at transesterification was done using both DMAP and stannous octanoate, this time after 10 mins the polymers were reacted with succinic anhydride which ring opens to form a carboxylic acid terminated polymer. The carboxylic acid should prevent transesterification by removal of the reactive alcohol groups. In gh17-87 there is already evidence of transesterification after 10 mins, but what is interesting in this case is that after the addition of succinic anhydride it appears that the mass peaks at 7 and 9 begin to decrease with time. After 80 minutes a peak of maximum intensity at 6 lactate units is visible above all others, transesterification is random and cannot explain this result. The question emerges as to what other mechanism might be at play in this reaction. A similar reaction has been carried out using DMAP as the catalyst – but the ESMS data are not yet available.

Although transesterification does not alter the stereochemistry of individual cations, it does allow the scrambling of tetrad sequences, unless only one lactate enantiomer is present. Despite being able to control the transesterification reaction by using shorter times, the polymerisation appears to have a wide polydispersity even after short reaction times. As yet, methods for narrowing this distribution, apart from by way of initiator to lactide ratios of 1:1, have not yet been discerned.

3.8 NMR evaluation of Poly(lactic acid) Alkyl Esters

Given the importance of PLA structure on the polymers physical properties, looking into how molecular structure might influence the surfactant properties was of interest. So looking at how the different catalysts could influence this was important and ^{13}C NMR spectroscopy was used as the method of tracking the tetrad sequences.

3.8.1 Short Chain Polymers and Tetrad Sequences

It is clear from the ^{13}C NMR spectra that there is no complete correlation between the tetrad sequences assigned in the literature and those obtained for the polymers in this instance. For L-lactide, we expect to see one peak at ~69 ppm which represent the *iii* tetrad sequences we can also see clearly the terminal methane carbon at ~67 ppm. What is seen instead, is that for stannous octanoate (gh17-03 and gh17-06) and triflic acid (gh17-02 and gh17-07) catalysed reactions we see 2 peaks at ~69 ppm. This does not indicate however, that racemisation has occurred. What is more likely is that due to the sensitivity of the methine carbons relative to the C-terminus (alkyl ester), that the neighbouring methine units have a different resonance to the methine carbons further down the polymer chain.

However, in the case of potassium hydroxide (gh17-01) it can be seen that racemisation and transesterification have occurred, as indicated by the presence of 4 peaks ~69 ppm, these peaks are probably from the sequences *sis, isi, iis* and *iss* since under transesterification conditions the probability of forming isotactic and syndiotactic tetrad sequences (i.e 4 lactate units with isotactic or syndiotactic junctions) on such a small PLA chain, we are unlikely to see *iii* and *sss* (only possible for meso).

3.8.2 DMAP Solution Reactions

In the case of DMAP solution reactions (see Table 5.5.1) *rac*-lactide was used. Here we see there are three peaks at ~69 ppm. In the literature, 2 peaks are expected for *rac*-lactide but this difference is explainable since in most papers molecular weights of polymers are usually over 20,000 Daltons and thus the ^{13}C NMR spectra

have to be done at much higher frequency (125 to 175 MHz) to improve the resolution. In this instance and at low molecular weights it is possible that there are three distinct methine (**C**H(CH_3)O) environments, at ~ 67 ppm we have the terminal methine and at 69.41 ppm we have the tetrad *iii, iis, sii* and *sis* and the extra peak at 69.71 ppm is likely to correspond to the methine carbon adjacent to the alcohol. My reasoning for this is that in the ^{13}C NMR spectrum, the methine resonances are sensitive to the C terminus (acid end), so the first two methine carbons will have a distinct resonance determined by their closeness to the alcohol. At high Mwt these environments become less distinct as their concentration is very low and we usually see only two distinct peaks at ~69 ppm.

3.8.3. Stannous Octanoate and DMAP melt reactions.

From the NMR evaluation of DMAP melts and stannous octanoate reactions with *rac*-lactide we usually see 4 peaks at ~69 ppm. In these instances the cause of this is transesterification (which can be seen from the mass spectra), this results in the possibility of forming tetrad sequences that are associated with *meso*-lactide. Again there are peaks attributable to the methine carbons neighbouring the C terminus for low molecular weight products. There is not enough data to explain which of these explanations is correct, but what is clear is that for a tetrad sequence to exist there must be at least 4 lactate units and in these reactions there is evidence of chain lengths of 4 and lower are produced, in this instance the characterising of tetrad sequences and stereochemistry may not be fully possible with these polymers.

In the case of gh17-80, a DMAP reaction with L-lactide was carried out and the peak distribution was looked at to determine whether DMAP is a strong enough base to initialise racemisation. In this case there are 3 peaks at ~ 69 ppm which suggests that racemisation does not play a significant role, since when this is compared to gh17-01 where racemisation has occurred which had 4 peaks. In this instance it seems likely that any extra peaks are attributed to the sensitivity of the methine groups to the C terminus and polymer chain lengths.

3.8.4 Tacticity

The tacticity of the polymers remains somewhat indeterminate, however, it is fair to assume that if no transesterification or racemisation (determined by NMR spectroscopy and mass spectra) is occurring then the tacticity may be assigned by what has already been established, L-lactide gives isotactic polymers and *rac*-lactide gives a heterotactic polymer.

Another likely problem with assigning the tacticity is due to polymer lengths in these cases. As tetrads are assigned from right to left and are based upon the previous unit, in the case of these short chains the tetrad sequences can become harder to define in regards to intensity as short chains promote less numbers for the sequence. For instance a PLA containing 12 LA units can only contain approx 6 tetrad sequences as the end of the sequence has its own characteristic peak at different ppm to the main chain.

3.9 Conclusion

The overall conclusion for this chapter is that PLA in sufficiently short chains does show some surfactant ability where the alkyl chain from the initiator is between 7 and 12 C atoms long. D,L-PLA has a better hydrophilicity than L-PLA due to the disorder in the chain making it more water soluble. Due to the polymer length and that heptanol, octanol and nonanol are cytotoxic these are unlikely to find any widespread use for any personal care applications. The other problem seems to be the rapid occurrence of transesterification that could lead to the scenario where there are PLA chains no longer attached to the long chain alkyl esters.

Where PLA does hold some promise however, is in that it might make an interesting hydrophobic tail, as it is still capable of some hydrogen bonding and has very strong interactions with itself. An investigation into possible polar head groups will be discussed in the next chapter.

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Chapter 4:

A Study of Poly(lactic acid) as a Hydrophobic Chain. Initiation of Lactide Polymerisation Using Polar Hydroxyl Containing Substituents.

4.0 Aim

To ascertain whether poly(lactic acid) is a suitable polymer to be used as the hydrophobic backbone of a surfactant molecule. This chapter will look at suitable hydrophilic initiators including reactions with sugars, choline chloride and copolymers with poly(ethylene glycol).

4.1 Introduction

From the previous chapter it was established that, in order to produce good surfactant activity, PLA chains could be no longer than around 12 LA units. This was due to the increase in hydrophobicity of PLA attributed to stronger interchain interactions as the chains got longer, as structurally PLA can pack quite efficiently, this was seen as D,L-PLA was more hydrophilic than L-PLA. This chapter will focus on the initial studies of poly(lactic acid) as a hydrophobic chain, where naturally occurring hydrophiles such as sugars and vitamins are used, as well as the common hydrophilic polymer poly(ethylene glycol) (PEG)

4.1.1 Polyesters a Well Known Hydrophobe

The hydrophobicity of polyesters is a widely cited property and almost all are considered to be hydrophobic. This can be taken account of by their everyday uses: from the synthetic polyester clothing we wear to the drinks bottles and food packaging, these polyesters are considered hydrophobic, water resistant etc. One of the most commercially valuable polyesters, poly(ethylene terephthalate) PET is regarded as an exclusively hydrophobic polymer and it is widely used in the production of drinks bottles. However, this is not strictly true. PET is normally prepared in a 2-step synthesis. The initial step is known as the *pre-polymerisation*

step is typically carried out either by tranesterification of dimethyl terepthalate and ethylene glycol or direct esterification between ethylene glycol and terephthalic acid [1], which produces lower Mwt polymers. The second step is high temperature polycondensation of the short chain polymers or oligomers carried out at ~ 280 ^{o}C. In PET synthesis water is either produced as a by-product or is used as a co-solvent to recrystallise terephthalic acid. The short chain polymer are capable of retaining a lot of this moisture thus the second step employs such high reaction temperatures both to insure complete water removal and to ensure a good polymer melt viscosity. There is a risk that any water present would result in hydrolysis during high temperature processing and this high temperature processing, results in a truly hydrophobic polymer.

The amount of water present in a polymer will depend on how the polymer is produced. Direct condensation esterification produces more water than transesterification and ring-opening polymerisation methods. Below is a summary of common methods available for polyester production:

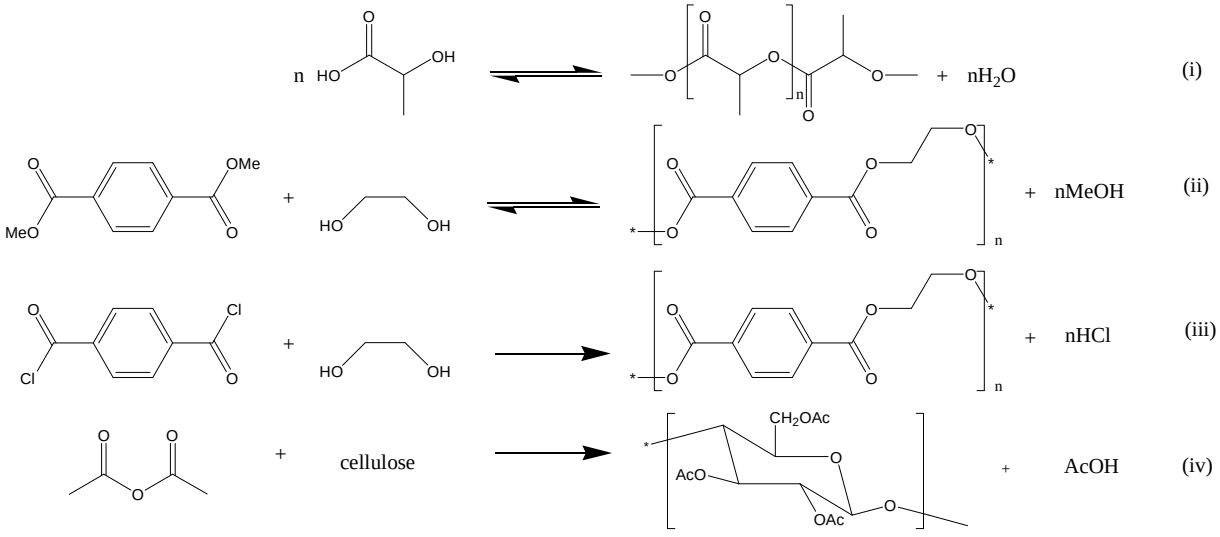

Figure 4.1.1. Common methods for polyester production.
Condensation (i), Transesterification (ii), via acid chloride (iii) and from anhydride (iv).

There are several other mechanisms for polyester formation, such as ring-opening polymerisation of cyclic anhydrides, as was discussed in depth in chapter 1; ring opening of epoxides and acidolysis are further methods often employed commercially in the production of polyesters. It can be argued that (iv) is not a true

polyester, but the differences between cellulose and cellulose acetate are considerable – cellulose is found in 100's of forms including wood, cotton and accounts for almost all plant structure. Cellulose acetate is a transparent polymer that is easily processable and easy to mould, it is commonly used for projector/camera films.

What largely accounts for the hydrophobic character in polyesters is how well they can pack together. Polyester chains are held together by a mixture of Van der Waals forces and electrostatic interactions between the dipoles of the carboxyl groups, and it is these electrostatic interactions that largely contribute to the physical properties of the polymer. L-Poly(lactic acid) is a highly ordered (crystalline) polymer that is brittle, but relatively easy to process. D,L-Poly(lactic acid) is a heterotactic polymer that is opaque, less brittle but softer than LPLA. Quite often in L-PLA preparation a small amount of the D-PLA or D,L-PLA (or meso lactide during polymerisation) are added to improve processability and physical properties of the polymer by reducing its crystallinity [2,3].

Poly(lactic acid) is generally considered for hydrophobic uses as it's short repeat units allow it to pack tightly together. Unlike PET, PLA is usually produced via ROP methods and therefore contains no residual water except perhaps trace amounts from side reactions or incomplete drying of lactide starting materials. As with PET and other condensation polymers any water present from the synthesis would be held by the polymer and at high T lead to hydrolysis.

4.2 Poly(lactic acid) Initiated using Dextrose, Sucrose and Sorbitol.

As a starting point in the search for hydrophilic initiators, with an emphasis on 'Green Chemistry,' naturally occurring materials for initiators seemed ideal, as such materials would have no detrimental effect in the wider environment. Sugars such as dextrose, sucrose and sorbitol are cheap, naturally occurring and hydrophilic molecules, their high water solubility is due to the presence of multiple hydroxyl groups. This poses something of a challenge in ROP with lactide as selective ROP at a particular site on the sugar is very challenging, and normal methods of sugar

protection such as acetylation, cannot be employed as the deprotecting method would be detrimental to the polymer.

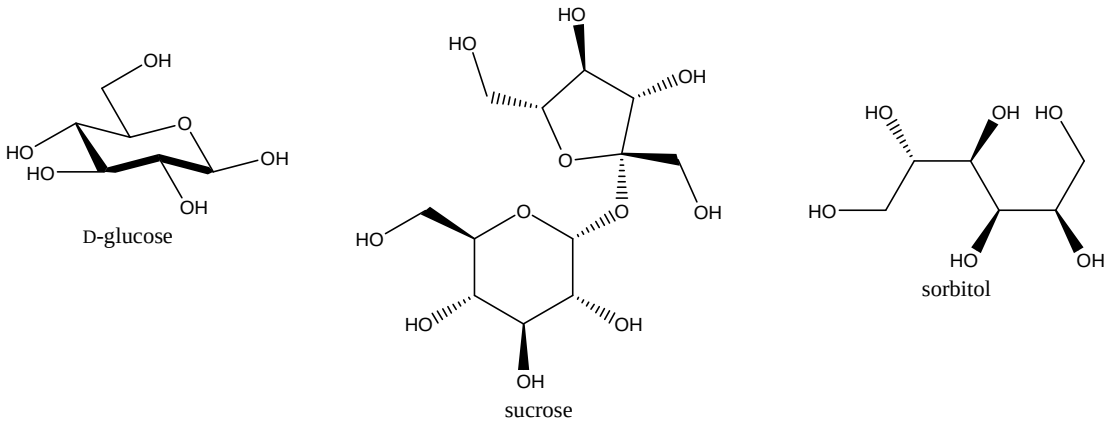

Figure 4.2 Molecular structures of 3 common sugars.

There are further problems with using these materials to initiate polymerisation of lactide. Sugars are unsuitable for melt polymerisations as they tend to burn/caramelise. Sugars also have a limited solubility and are only soluble in polar solvents such as water, alcohols, DMSO and other highly polar solvents. Water and alcohols could not be employed as solvents as they would react with lactide, though an acetone\water mixture had limited success, but chain lengths were very short.

4.2.1 The Melt Polymerisation

In the melt polymerisations of dextrose or sucrose with lactide there was no evidence of having initiated the polymerisation. The only peaks to register in the ^{13}C NMR spectrum belong to short chain PLA. In this reaction the catalyst ($Sn(oct)_2$) has led to the decomposition of the dextrose causing it to brown during the reaction conditions. This was confirmed by heating up two samples of dextrose to the reaction temperature one containing catalyst the other without. The sample containing catalyst browned much faster (within 2 minutes) and the one without decomposed far slower under thermal conditions. The browned remains could not be analysed by NMR spectroscopy as they were insoluble in almost all solvents attempted. What was also noted from the NMR spectrum of the melt was the presence of free 2-ethylhexanoic acid, as indicated by the weak signals between ~23 ppm and 32 ppm (CH_2). This can occur for either of two reasons:

a) A more stable tin alkoxide or carboxylate forms, or

b) The tin catalyst forms stannous hydroxide as an intermediate, as under the reaction conditions it eventually forms stannous oxide.

4.2.2 The Use of Water as a Cosolvent

In order to overcome the solubility problems associated with sugars, water was employed as a cosolvent in varying amounts. Like alcohols water is a far from ideal solvent as it acts as a nucleophile and can also speed up side reactions such as transesterification.

What was evident in all cases where water was used as a cosolvent was that mostly short-chain PLA was produced independently of initiator or that it reacted at nearly all sites of the initiator. However, in one experiment the PLA looked to have reacted on only some of the secondary alcohol sites, leaving the primary alcohol unreacted (see Figure 4.2.1).

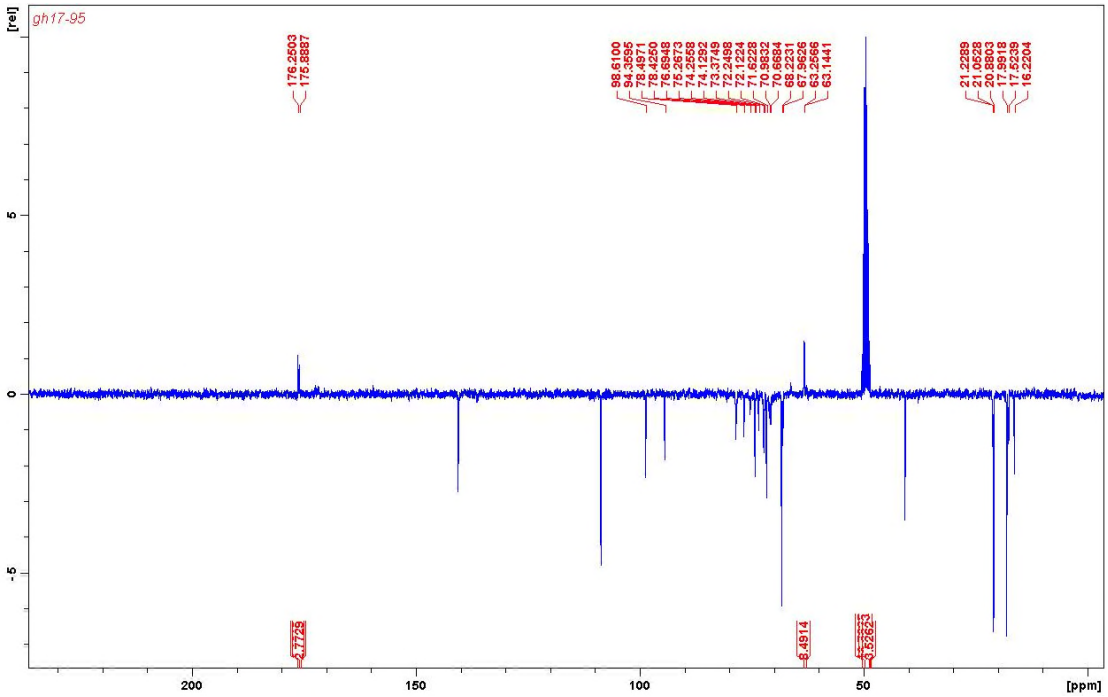

Figure 4.2.1 ^{13}C NMR spectrum of polymer initiated by dextrose in a DCM/H_2O system.

There are several areas of note in this spectrum. To begin with the clusters of peaks from 63 ppm to 98 ppm, these correspond to both PLA and dextrose signals,

but the PLA signals are easily differentiated from those of the sugar, although the sugar peaks are more difficult to resolve. The peak at 67 ppm are the PLA end group methine carbons and the size of this peak compared to the peaks at 70 ppm (PLA methine groups from chain) show that short chains are being produced.

An interesting peak is at ~63 ppm, this shift along with its orientation, indicates this is the free primary alcohol on dextrose and the very small peak ~65 ppm is where there has been some small amount of ester formation.

The rest of the dextrose peaks are slightly shifted and there are more peaks than expected. A normal sample of the dextrose (analysed by NMR spectroscopy) has 9 peaks between 69 ppm and 95 ppm representing the 6 C environments over the two enantiomers. In the spectrum at least 13 peaks are present for dextrose. Therefore indicating that there is some randomisation on the sites where there is ester formation. What this tells us is that there is a mixture of possible PLA molecules within the sample, as there are 5 possible sites for the initiation of lactide polymerisation over the dextrose molecule, the spectrum is likely to represent a mixture of mono to penta-substitution by PLA chains.

It can also be deduced that transesterification has occurred rapidly throughout this reaction (due to water presence). The peaks at 175-176 ppm are the free acid peaks of PLA or lactoyl lactate. All lactide has been consumed in the reaction as it has distinct peaks at 72.48 ppm and 15.71 ppm. These results agree with the transesterification mechanism suggested by Hedrick *et al.* [4], when DMAP was used as a catalyst. They discovered that during transesterification secondary alcohols were dormant to reactions with ring-opened products and that chain transfer was only seen with primary alcohols. Therefore, as transesterification is a reversible pathway, when a secondary alcohol ring opens lactide it is more stable to chain transfer at that position, but cleavage can occur readily at the primary alcohol. The added complication with water present in the system is that hydrolysis occurs as well as transesterification leading to production of a carboxylic acid terminated PLA. In this particular reaction water was a cosolvent with DCM and ran as a biphasic system at 45 ^{o}C (1 : 2, water : DCM.)

4.2.3 Reactions in DMSO

After checking a wide range of solvents, DMSO (dimethylsulfoxide) and DMF (dimethylformamide) were the only solvents polar enough to solubilise the sugars. DMF and DMSO are far removed from green solvents, DMF is toxic to the reproductive system and possibly carcinogenic, DMSO has a low toxicity but can be difficult to remove and can decompose to dimethylsulfide, which is an unpleasant smelling solvent. A problem was the removal of DMSO from the polymer at the end of the reaction. The high boiling point of DMSO (b.p 189 ^{o}C) meant that it had to be removed under reduced pressure, which coupled with reaction temperature could depolymerise any short chain PLA back to lactide.

The results with DMSO showed little improvement over the other methods of solubilising sugars. Short chain PLA was a common by-product in these reactions but the initiation by these sugars in DMSO resulted in more of the sugar attached to the PLA chains. The ESMS data show up to 10 units were incorporated; what is odd, however, is that the separation is predominantly 144 amu, but the ^{1}H NMR spectrum suggests that incorporation occurred over a wide range of sites. What is strange is that there is only 1 very weak peak where the primary alcohol (CH_2-OH) is expected in the ^{13}C NMR spectrum (Figure 4.2.3) taken from a sucrose initiated reaction. Here it appears that no reaction took place at any of the primary alcohols, which would have been expected, as they are the more nucleophilic. The only explanation for this would be that the primary alcohols strongly interact with the DMSO solvent, making it an unfavourable site for lactide polymerisation.

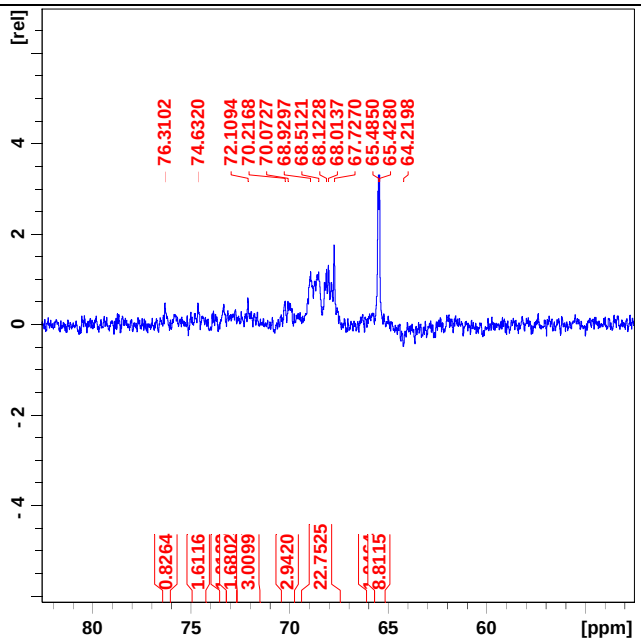

Figure 4.2.3 An enhanced view of the methine region in the ^{13}C NMR spectrum of a polymer prepared in DMSO using sucrose as the initiator in the presence of tin octanoate.

The small peak at 64.21 ppm is from the primary alcohol (pointing down in PENDANT), that 67.72 ppm arises from the PLA end groups and the cluster of peaks at 70 ppm is from PLA (indicating very short chains). The resulting polymer however was not very soluble in water and showed little, if any, surfactant ability.

In order to produce the type of surfactant ability wanted from these reactions, the traditional surfactant model needed to be considered. The traditional surfactant is linear, with a polar head and long tail. From the reactions thus carried out using sugar initiators, it appears as though the primary products are star-shaped polymers with multiple branches off a single core. These could work as emulsifying agents, but with each branch added and the length of each branch increasing, the water solubility of the polymer is reduced. There is, thus, less chance of water molecules interacting with the hydroxyl groups at the core.

To be able to selectively react lactide at a desired position there are only two methods available. The first, mentioned earlier, is to protect and then deprotect the sugar. The second route, which is largely unexplored, is to use highly selective enzyme catalysts that react solely at the primary alcohol. There has been some success in using Lipase enzymes (Candida Antarctica Lipase B) for the selective

esterification of carbohydrates [5]; but for ROP of lactide the enzymes so far noted are lipase PS (Pseudomonas fluorescens) [6]. The decision was made that investigating this possible path would not be an efficient use of time, as there were still many possible polar initiators to be tested.

One of the factors in the successes and failures of lactide polymerisation initiated by sugars seems to have been the presence of water. Drying sugars is a difficult process, as heating under vacuum can lead to decomposition. Drying overa desiccant (such as P_2O_5) seemed to offer the best method of drying, but, as several of the experiments used water as a co-solvent, it was unnecessary.

Considering the problem in retrospect (having further studied new relevant literature), there are several possibilities that could have been attempted. Ionic liquids have been produced to be used as solvents as they have been shown to have good carbohydrate solubilities [7], though adding the problem of solvent removal. Some sugars will form eutectic mixtures if mixed with the right salt. From my own experiments a 3 : 1 ratio of dextrose to choline chloride will form a eutectic mixture, but it is very viscous, and the choline chloride would probably react preferentially with the sugar, due to its own primary hydroxyl group. An alternative catalyst system may also work. Some solid acid catalysts or clays [8] are known to preferentially react with primary alcohols of sugars as well as carry out lactide polymerisation, but a brief study with Montmorillonite clay showed slow polymerisation and difficult product recovery requiring many washes with volatile organic solvents.
Due to the inherent problems of solubility and selectivity with the sugars, a cheap, simple and environmentally friendly method of these reactions was not found.

4.2.4 Methods for Preparing Sugar Initiated Poly(lactic acid)

Materials:
Dextrose, sucrose and sorbitol were procured from the department chemical stores. All were dried over phosphorus pentoxide under vacuum prior to use.
D,L-lactide was purchased from Aldrich and dried by sublimation prior to use, except where water was used as cosolvent.

DMAP and Tin (II) ethylhexanoate catalysts were purchased from Avocado and Aldrich respectively and used without further purification.

DMSO and acetone were purchased from Fisher chemicals and DMSO stored over molecular sieves prior to use.

4.2.4a Melt Polymerisation Using Sugars:

In a clean dry round bottom flask, the dry lactide was heated to molten (~130 ^{o}C) before the sugar was added. The catalyst was added once the sugar had gone into the melt. This was carried out in ratios of 6:1 (lactide to initator; L : I) up to 12 : 1. The reaction was allowed to proceed for 20 minutes. The products were analysed by ^{13}C NMR spectroscopy using $CDCl_3$, d_4-methanol or D_2O as solvents dependent on the solubility and molecular weight distribution was obtained from ESMS.

Results:

Table 4.4.2a Shows results of DMAP reactions carried out in the melt.

Initiator	Ratio (L : I)	Catalyst	Mwt Distribution (LA units)[#]	Free OH- sites
Dextrose (94)*	3 : 1	$Sn(oct)_2$	4 – 8	N/A
Sorbitol (101)	6 : 1	DMAP	2 – 6	N/A

[#] Mwt Distribution given in lactic acid units (LA)* Numbers in parenthesis are indicative of the experiment number.

4.2.4b General Method Where Water/Organic was Solvent:

To a clean dry round bottom flask, sugar and lactide were added in controlled ratios ranging from 1:3 up to 1:10. To the mixture acetone/DCM and water were added in ratios of 2:1 to 5:1 (total volume ~ 50 ml) and heated to between 45 and 80 ^{o}C with stirring before the catalyst DMAP (5 mmoles) was added. High catalyst amounts were required for the reaction to run efficiently, and in most cases for lactide polymerisation the DMAP catalyst was used in a 4:1 ratio with initiator [9]. In these reactions at most a 1:1 ratio of catalyst to initiator was employed. The reactions were allowed to proceed from 6 to 24 hours before the solvents were removed on a rotary evaporator. The products were analysed by NMR spectroscopy and ESMS.

Results:

Table 4.2.4b Shows the results for reactions where water was used as cosolvent.

Initiator	Cosolvent	Ratio (L : I)	Conditions	Mwt Distribution (LA units)
Dextrose (96)	Acetone	6 : 1	60 ^{o}C; 4 hrs	0[a] - 11
Dextrose (97)	Acetone	10 : 1	60 ^{o}C, 6 hrs	2 – 6
Dextrose (95)	DCM	3 : 1	45^{o}C; 4 hrs	N/D
Dextrose (100)	Acetone	25 : 1	60 ^{o}C, 24 hrs	4 – 12 6 – 12 PLA
Sucrose (102)	Acetone	9 : 1	60 ^{o}C, 5 hrs	2 – 4
Sorbitol (101b)	Acetone	6 : 1	88^{o}C; 6 hrs	4 - 8

[a] 0 is indicative of free initiator.

4.2.4c General Method when DMSO was used as a Solvent

To a clean dry round bottom flask, sugar and lactide were added in controlled ratios. Then dimethylsulfoxide (DMSO, 50 cm^3) that had been stored over molecular sieves prior to use, was added with stirring until solids had dissolved. The reaction mixture was heated to 70 ^{o}C and, once the catalyst (DMAP or *p*-toluenesulfonic acid (p-TSA)) was added, was allowed to react for 6 h. The DMSO was removed by distillation (69 ^{o}C, 5mm Hg) and the polymer recovered and analysed by NMR spectroscopy and ESMS.

Results:

Table 4.2.4c Shows the results where DMSO was used as solvent.

Initiator	Ratio (L : I)	Catalyst	Conditions	Mwt Distribution (LA units)
Dextrose	3 : 1	DMAP	70 ^{o}C; 6 hrs	4 - 10
Dextrose	3 : 1	DMAP	RT; 18 hrs	4 - 10
Dextrose	3 : 1	p-TSA	40 ^{o}C; 4 hrs	_
Sorbitol	6 : 1	DMAP	70 ^{o}C; 6 hrs	_

4.3 Reactions using Choline Chloride as a Hydrophilic Initiator in Lactide Polymerisation.

Choline is a naturally occurring material that is commonly found as one of several salts. Choline chloride (2-hydroxyethyltrimethylammonium chloride) is a naturally occurring chemical found in animal tissue and plant cells as a constituent of lecithin, it is considered a B-vitamin precursor. It is artificially added to animal feeds and taken as a diet supplement that can be purchased from health food shops. Choline has three main roles in physiology:

1) Used in cell structure and for signalling in cell membranes
2) In neurotransmission (acetylcholine synthesis)
3) As a source of methyl groups via betaine (metabolite).

It is a dietary source of trimethylamine and when wet or digested in large quantities gives off a fishy odour. Choline chloride is of interest as it has structural features that would apparently make it ideal in the preparation of PLA based surfactants.

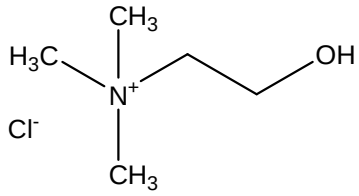

Figure 4.3. Molecular Structure of Choline Chloride.

Quaternary ammonium salts have widespread use in the surfactants industry and are characteristic of being stable to pH changes – meaning water solubility is maintained in acidic, neutral and alkaline solutions. They have found widespread use as dye transfer inhibitors, fabric softeners and in personal care applications such as hair conditioners and soaps. They also exhibit antibacterial properties, which make them ideal for use in the making of dishwasher detergents.

4.3.1 Choline Chloride Reactions in ^{t}BuOH

Like the sugars, choline chloride is insoluble in most organic solvents, except for those with which it can coordinate. Alcohols and organic acids are the best solvents for using choline chloride but are unsuitable as alcohols will react with lactide and used as a solvent, they could lead to rapid transesterification and reaction death by end capping the polymer. However, tertiary alcohols are not nucleophilic enough to act as initiators in lactide polymerisation so 2-methyl-2-propanol (^{t}BuOH) was chosen.

This led to one further issue in that $Sn(oct)_2$ could no longer be used as a catalyst as it would form a stable alkoxide with the solvent and no longer be reactive. DMAP was therefore used in all choline chloride reactions in solvents.

There were two main problems to arise with this system; the first seems to be that ^{t}BuOH saturates the catalyst, increasing the reaction time. In nearly all cases the conversion of lactide was low with M_n values never exceeding the expected values; for a reaction at 20 : 1, the M_n would be expected to be ideally 40 LA units, but in this case does not exceed 25 LA units. The second problem is the removal of the solvent. Several methods were attempted but the only reasonable method was to remove the solvent on the rotary evaporator. Although PLA polymers are (usually) not soluble in diethyl ether, it was unsuitable for precipitation purposes as in the presence of tBuOH nothing precipitated. Therefore removal under reduced pressure offered the only viable method, although a small quantity of ^{t}BuOH was retained in the polymer.

The surfactant behaviour of the ^{t}BuOH polymers was reasonable in the cases where there was little to no free PLA chains. The experimental and results for this can be seen in section 4.3.6a.

4.3.2 Choline Chloride Deep Eutectic Mixtures

Choline chloride has high melting point (305 ^{o}C) and is a white crystalline hygroscopic salt that has a variety of useful properties. Abbott and co-workers [10] established that, by using choline chloride along with mixing a variety of organic or

inorganic materials, they could form deep eutectic mixtures. A deep eutectic mixture is formed when two or more compounds are mixed (sometimes with heating) and interact (usually involving hydrogen and ionic bonding) to form a liquid with a very much lower melting point than any of its components but without any change in chemical composition of the starting materials. These deep eutectic mixtures show the same sort of solvation properties as other ionic liquids (such as the imidazolium salts) in that they have no vapour pressure and can solubilise a wide range of organic and polar materials. There are several examples of eutectic behaviour the most common being salt used to melt ice/snow on roads in winter; here the salt interacts with the water producing a liquid with a lower melting point. Figure 4.3.2a illustrates one of the eutectic mixtures formed.

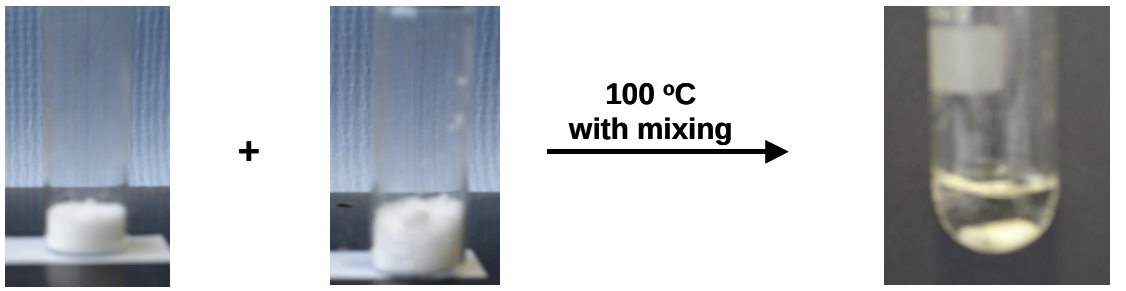

Figure 4.3.2a Deep eutectic mixture of citric acid (m. pt. 153 ^{o}C) and choline chloride (m. pt. 305 ^{o}C) (1 : 1) showing white crystalline solids before and a liquid after mixing >100 ^{o}C.

Several groups have investigated deep eutectic mixtures for a variety of uses such as suitable ionic liquid solvents for catalytic reactions, for reactions of carbohydrates and as template solvents for porous materials such as in preparing zeolites, or metal organic frameworks. A further example being explored arises because these materials offer relatively simple methods of adding chirality to a system and therefore may be useful solvents in a variety of asymmetric type reactions.

Table 4.3.2 illustrates some of the possible eutectic mixture combinations with choline chloride and whether any attempt at a polymer was made, the eutectic mixtures used and their effectiveness in producing polymers with lactide.

Table 4.3.2 Shows the results for choline chloride reactions where choline chloride was in a eutectc mixture, for melt polymerisation.

Component	Eutectic Mixture Ratio[a]	Ratio (L : I)	Catalyst	Mwt Distribution (LA units)
Citric acid	1 : 1	6 : 1	$Sn(oct)_2$	_
Tartaric acid	2 : 1	_	_	_
Dextrose	2 : 1	_	_	_
Urea	1 : 1	6 : 1	$Sn(oct)_2$	_
Urea	1 : 1	10 : 1	-	5 – 34 LA units
Urea	2 : 1	10 : 1	-	4 –36 LA units
Urea	3 : 1	10 : 1	-	3-30 LA units
Zinc chloride	1 : 1	6 : 1	-	_

[a] Ratio is expressed as component : choline chloride.

Zinc (II) chloride is known as an initiator for lactide polymerisation, if not a particularly good one. Zinc chloride is a strong lewis acid and acts usually by forming a zinc alkoxide which then acts as the main catalyst species. The problem is that it is possible to form some HCl, which, if present with any water, can lead to hydrolysis of poly(lactic acid). Zinc chloride/choline chloride eutectic mixtures did not work well. It was able to convert nearly all the lactide to poly(lactic acid), but the polymer showed no indication of having reacted with choline chloride and was a black and tarry resinous mass with no water solubility. The polymer chains were short indicating the prevalence of unwanted side reactions.

The best eutectic mixtures for the polymerisation of lactide were found to be those containing urea. The reason is perhaps that urea/choline chloride have been found to be among the best eutectic mixtures for a variety of uses and they have low melting points and, therefore, a lower viscosity. Compared with the polymer melt they are much more mobile. It also may be worth noting that urea may also act as a co-catalyst in the reaction mediating the interaction of the catalyst with the initiator. The polymers produced by this method looked to have good polymer distributions in the mass spectra.

Among the polymers produced were those where no catalyst was added. The Urea/Choline chloride mixtures seem to be capable of ROP. It is debateable as to

which was the most efficient as by the MALDI-TOF, the 2:1 mixture was better than 1:1, but there was no clear advantage in using the 3:1 mixture. However, when looking at the ^{1}H NMR integrals, the ratio of PLA end groups to choline chloride are 2:1 for 1:1 ChCl/urea and 3:1 for the 2:1 and 3:1 ChCl/urea. Due to this the M_n values are not accurate for the final product. There was some unreacted lactide in all cases, but the very low M_n values can only have come as a result of lactic acid dimer (lactoyl lactate) being present in the products. This dimer may arise because of water residues reacting with lactide. The rate of the polymerisation is comparable to the systems where $Sn(oct)_2$ has been used. Overall, this indicates that urea is important in the reaction and may in this situation improve the nucleophilicity of the choline chloride, or it may act simply as a mediator between choline chloride and lactide.

As a note, in the MALDI-TOF mass spectrum there were some very minor peaks that may have indicated urea bound to PLA. This could be due either to the formation of small amounts of urea-terminated polymer, or illustrates a strong H-bonding interaction between urea and PLA.

Work by Hedrick *et al.* [11] on an organic catalyst for lactide polymerisation used a multi-component thiourea-amine catalyst Figure 4.3.2b. On testing this catalyst they also carried out the reaction using just the individual components. In lactide polymerisations the thiourea was responsible for holding the lactide rings in place through H-bonding. It may be that urea hydrogen bonds to choline chloride and is able to facilitate the polymerisation by being able to hold lactide molecules in a similar manner.

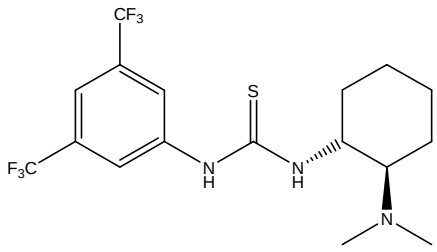

Figure 4.3.2.b: Thiourea catalyst used in ROP of lactide [11].

In order to ascertain urea's ability as an initiator and to see whether it could ring open lactide rings, a reaction was carried out without choline chloride but with the tin (II) catalyst. Urea is a difficult molecule to monitor by NMR spectroscopy as the carbonyl peak is very weak, and NH and NH_2 interactions are only visible in the

^{1}H NMR spectrum. The ^{1}H NMR indicates the presence of free urea (~ 5.7 ppm) in the system. However, there are some minor peaks in the region expected for an amide link around 8.9 ppm and 10.25 ppm which are only visible when urea is present in the systems. The polymer initiated by urea also shows a reasonably good conversion of lactide, with an impressive M_n of 18 LA units (initiator to lactide ratio of 5.6 : 1), much higher than when choline chloride was used as an initiator. The MALDI-TOF (Figure 4.3.2c) spectrum confirms the presence of urea bound PLA, however the main peaks result from free PLA. The high M_n and the distribution pattern of 7 to 34 LA units suggest that urea is not responsible for transesterification, and perhaps may act to inhibit it.

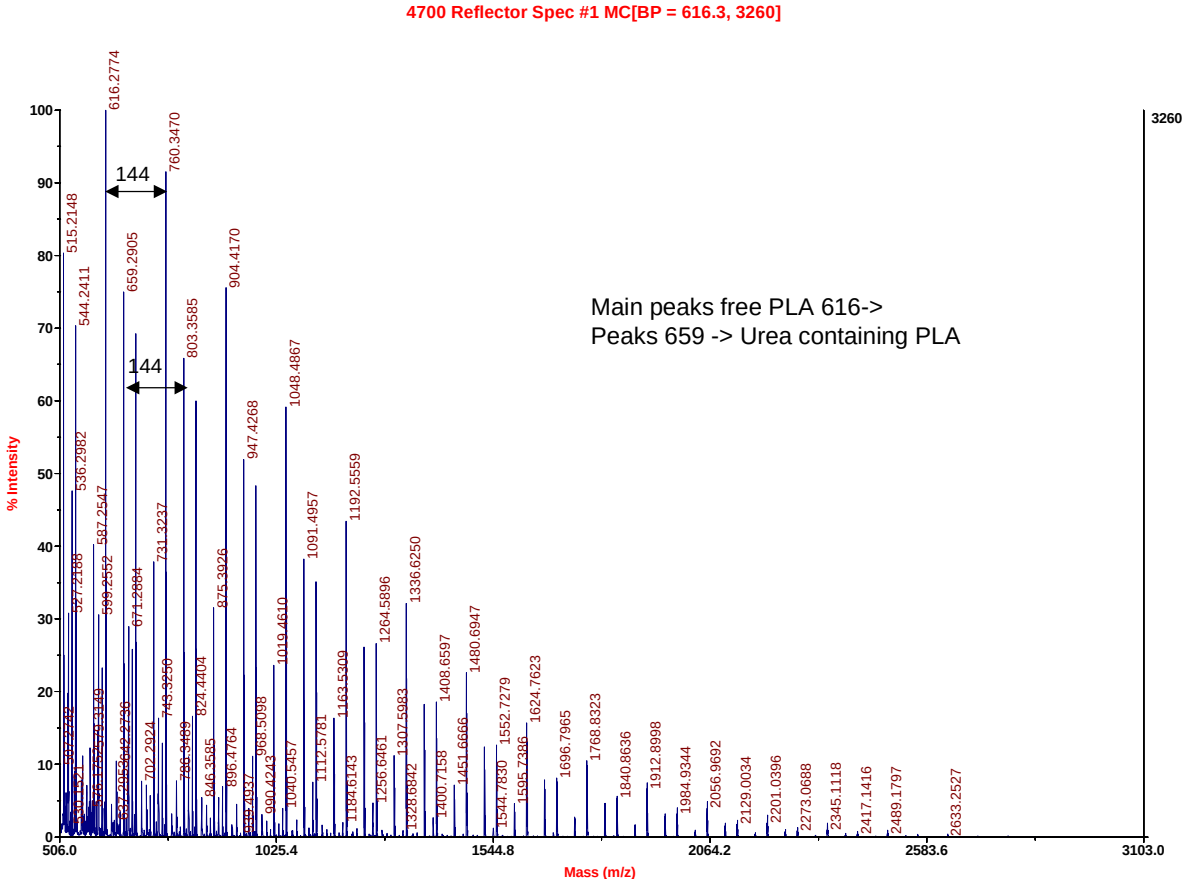

Figure 4.3.2c: MALDI-TOF of Urea initiated PLA; the major peaks 616-2633 with mostly 144 amu separation are free PLA, the other peaks 515 - ~2373 are Urea bound PLA with 144 amu separation.

What was apparent in the reactions where no additional catalyst was used is that there is little to no free PLA, as shown by the fact there are no free acid peaks near 170 ppm in the ^{13}C NMR spectrum and there is little evidence for free acid in the MALDI-TOF. The conversion of lactide is not, however. very high, as indicated by

integral heights in the ^{1}H NMR spectrum. When choline chloride is a free molecule the overall effect is that the OH is very nucleophilic since choline chloride is always used up in the reaction. The effect when the ester forms however, suggests that once the polymer reaches a certain length the $^{+}NMe_3$ has an overall electron withdrawing effect making the reactive alkoxide chain end less nucleophilic the closer it is to the choline end, but more importantly making the carbonyl carbons more electrophilic than the carbonyls of lactide increasing the likelihood of transesterification. The result is that there is little free polymer (COOH terminated PLA) but this consists of very short chains and poor lactide conversion. The structure below (Figure 4.3.2d) shows the likely effect of choline chloride on the polymer.

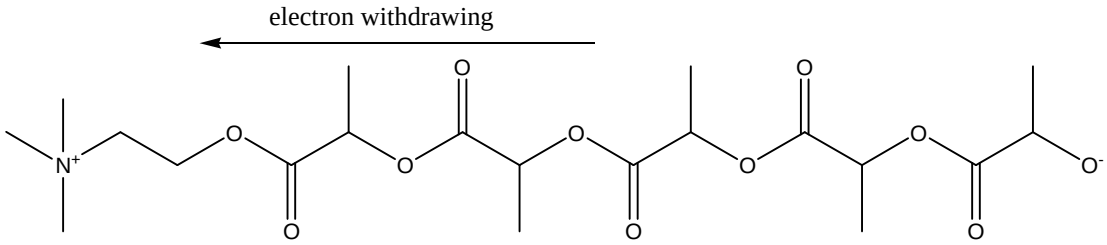

Figure 4.3.2d. Effect of Choline Chloride on Polymer.

In one of the early choline chloride : urea reactions a narrow polydispersity was noted in the MALDI-TOF mass spectrum; even though the M_n value was low (8 LA units) figures 4.3.2d and 4.3.2e there were no visible peaks before ~8 LA units in the spectrum. It may be that when urea is used in combination with choline chloride the electrostatic and H-bonding interactions occurring from the eutectic phase reduce this electron withdrawing effect improving ROP of lactide and reducing the amount of transesterification early in the reaction.

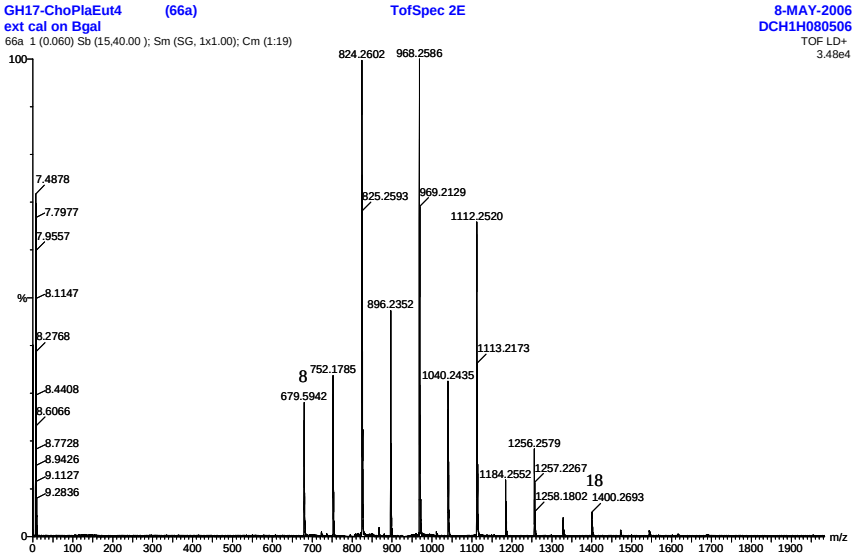

Figure 4.3.2d. Narrow polymer distribution from choline chloride : urea initiated poly(lactic acid) at 6 : 1 L : I ratio.

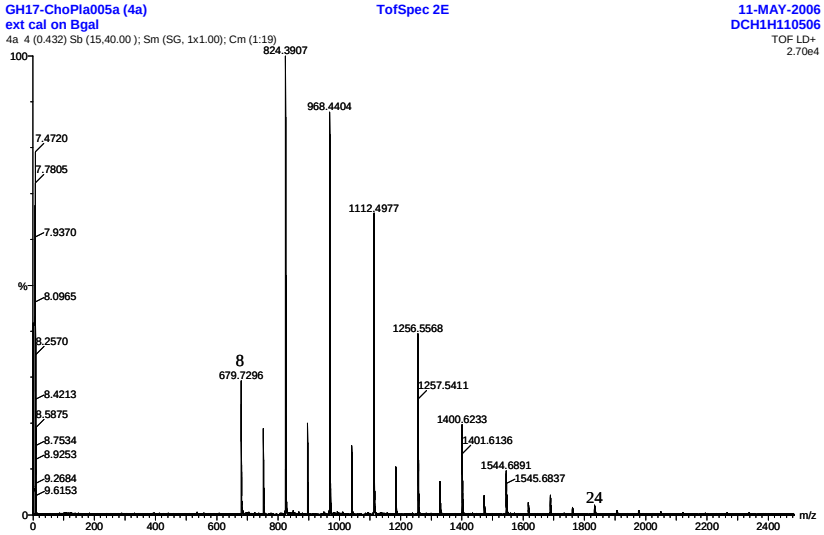

Figure 4.3.2e. Narrow Molecular weight distribution for choline chloride : urea initiated PLA at 12:1 L : I ratio.

4.3.3 Choline Chloride Direct Melt Reactions

It was found that, as long as the choline chloride to lactide ratio was more than 1:6 choline chloride would dissolve at 130 ^{o}C reaction temperature. The main problem with choline chloride in the melt was the mobility of the initiator. In bulk samples, especially, very little choline chloride reacted with lactide and the reactions often led to colour changes from clear to brown – indicating transesterification etc with only up to 45 % of the substrate converted. L-Lactide was especially difficult to use in melt reactions. It is conceivable that some HCl may be produced in the

presence of any residual moisture. The presence of this would actively work against the formation of new PLA chains leading to hydrolysis, although more likely it would simply be expelled from the melt. However, the formation of choline hydroxide would lead to a fast transesterification catalyst, which could act counter-intuitively to the stannous octanoate or DMAP catalysts employed.

Even with the melt reactions several methods were attempted to improve the reaction yields and polymers. One of these cases was to ROP at 130 ^{o}C for 5-45 minutes then dissolve in an organic solvent such as THF or toluene (to improve mobility) and allow to react for longer at a lower temperature. The hope was that this would reduce transesterification and increase mobility. In actuality there were no real advantages in this method. In the case where toluene was used as a solvent the solution often appeared cloudy, indicating incomplete solubility or some micellar formation where the choline chloride is inside the micelle and PLA tails outside and this phenomena may not be beneficial with regard to chain extension by further ROP of lactide.

4.3.4 Surfactant and Emulsification Behaviour of Choline Chloride Initiated Polymers

Choline chloride containing polymers are the most hydrophilic of all the surfactants synthesised during this project. That is not to say that they have shown the best surfactant behaviour or the best emulsion behaviour, or that they are easy to work with. In fact the hydrophilic nature of these polymers makes them notoriously difficult to work with. They are often soft especially where D,L-lactide has been used and they cannot be easily ground into powder, without becoming wet and sticky.

4.3.5 Conclusion

From the results in lactide polymerisation it seems that the eutectic mixtures offer the best methods of producing PLA with or without catalyst. The eutectic mixture negates the problems associated with direct melt and solution based methods. The eutectic method is not however without it's flaws, the conversion of lactide is still not complete and transesterification still occurs, though fortunately with minimal free

PLA chains. In the future these polymers could be improved by combining the eutectic method with a solution method and use chain extension to get longer PLA chains.

It is entirely possible that in future work it may be more feasible to produce long chain PLA and then graft choline chloride to the polymer by esterification or transesterification with DMAP catalyst, rather than by initiation with choline chloride.

4.4 Methods for preparing Choline Chloride initiated polymers

In this section the polymerisation methods, details and results for choline chloride initiated polymerisation are recorded.

4.4.1 Materials

Materials:

Choline chloride was purchased from Fisher chemicals and recrystallised from boiling ethanol 3 times before filtering and drying in a vacuum desiccator over phosphorus pentoxide for 48 hours prior to use.

Lactide was purchased from Aldrich and dried by sublimation prior to use.

Urea was purchased from Aldrich and ground down to a fine powder using a mortar and pestle before storing over P_2O_5 prior to use.

Citric acid and zinc chloride were purchased from Fisher chemicals and used as received.

DMAP and $Sn(oct)_2$ were purchased from Avocado and Aldrich respectively and used without further purification.

2-methyl-propan-2-ol (t-butanol) was purchased from Aldrich and distilled over potassium carbonate prior to use.

4.4.2 Choline Chloride Reactions in ^{t}BuOH

To a clean dry round-bottomed flask lactide, ^{t}BuOH and DMAP are added and heated to 85 ^{o}C, before choline chloride is added. The reaction was allowed to proceed for 6 hrs. When the reaction was complete the ^{t}BuOH was removed on the rotary evaporator. The resulting polymer was then analysed by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry.

In the case where the polymer was sufficiently water soluble, its surface tension was measured at 25 ^{o}C with a concentration of 1 mg ml^{-1} using a Nima 9000ST manual surface tensiometer. The surface tensions given below are averaged over 4 runs.

Results:

Table 4.4.2 Shows results for choline chloride reactions carried out in *t*-butanol

Ratio L : I	Mwt Distribution (LA units)	Separation (amu)	M_n (LA units)	Surfactant quotient [a]	Surface Tension (mN/m)
10 : 1	2 – 6 (ESMS)	144	_	3	
20 : 1	4 – 32	144	<25	4	43.1
15 : 1	2 – <40	144	<20	5	49.27
6 : 1	8 – 28	144	6	3	_
3 : 1	1 – 25	144 + 72	9	3	_
15 : 1[b]	3 – >38	144 + 72	10	2.5	_
15 : 1[b]	3 - 20	144	16	_	_

[a] Surfactant quotient as given in the previous chapter is an observation where solubility and foaming are graded on a 5-point scale and then an average taken. A result of 5 indicates complete solubility and high foaming. [b] This was a sample that was prepared in bulk.

4.4.3 Choline Chloride Direct Melt Reactions.

To a clean dry round bottom flask dry lactide and dry choline chloride were added and heated to 130 ^{o}C until molten. The catalyst was then added and the reaction proceeded for 20 to 40 minutes, noting any changes in colour resulting from high transesterification. The polymer was then analysed by ^{1}H and ^{13}C NMR

spectroscopy and MALDI-TOF mass spectrometry. Where the polymer was sufficiently water soluble, the surface tension was also recorded.

Results:

Table 4.4.3 Shows results for choline chloride direct melt reactions

Ratio	Mwt Distribution (LA units)	Separation (amu)	M_n (LA units)	Surfactant quotient	Surface Tension (mN/m)
10 : 1	8 – 28	144	15	5	40.2
20 : 1	8 – 34	144	19	5	40.75
20 : 1	8 – 40	144	_	5	_
15 : 1	_	_	12	3	_
15 : 1	_		10	4	_
20 : 1[a]	_	_	^{13}C only	4	_
20 : 1[b]	_	_	^{13}C only	4	_
20 : 1[c]	_	_	^{13}C only	4	_
6 : 1[d]	3 – 24	144	6	4	_

[a] Run for 10 minutes at 130 ^{o}C, then dissolved in THF and allowed to react for 2 hrs @ 80 ^{o}C; [b] Ran for 45 minutes at 130 ^{o}C, then dissolved in toluene and allowed to react for 90 minutes; [c] Run for 5 minutes @ 130 ^{o}C, then dissolved in toluene and ran for 3 hours.

4.4.4 Choline Chloride Eutectic Mixtures as Initiators With or Without Addition of Catalyst

Preparation of eutectic mixtures.

To a clean dry quick-fit tube or the reaction vessel (round bottomed flask) equipped with a stirrer bar choline chloride and the other additive (urea, zinc chloride or citric acid) was added and heated to 130 ^{o}C with stirring until molten, occasional manual blending using a glass stirring rod was required where the ionic liquid was highly viscous. The eutectic mixture was usually formed in less than 20 minutes. The liquid formed was then placed under vacuum for 2 hrs to remove any traces of water. The general trend as regards viscosity was that the ratio of counter salt to choline chloride should be 2 : 1 or 3 : 1 having lowest viscosity. A ratio above 5 : 1 usually leads to saturation and no liquid formation.

4.4.4a Preparation of PLA with Eutectic Mixture.

To the pre-prepared dry eutectic mixture (1 : 1) ratio unless otherwise stated, lactide was added at 130 ^{o}C and catalyst (DMAP or $Sn(oct)_2$) was added once the mixture was molten. The reaction was allowed to proceed for 20 – 60 minutes and the resulting polymer analysed by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry.

Results:

Table 4.4.4a Shows the results obtained for reactions with Choline chloride in a eutectic mixture showing the make-up of the eutectic mixture and the catalyst used.

Ratio L : I : E	**Catalyst**	**Eutectic Mixture**	**Mwt Distribution (LA units)**	**Separation (amu)**	**M_n (LA units)**	**Surfactant quotient**
3 : 1 : 1	DMAP	Citric acid	N/D	N/D	N/D	2
6 : 1 : 1	DMAP	Citric acid	N/D	N/D	N/D	2
6 : 1 : 1	_	Zinc chloride	_	_	_	_
6 : 1 : 1	$Sn(oct)_2$	Urea	8 – 22 LA's	144	8	5
12 : 1 : 1	$Sn(oct)_2$	Urea	_	_	10	4
3 : 1 : 1	$Sn(oct)_2$	Urea	_		5	5
10 : 1 : 1	_	Urea	5 – 32 LA	144	10	5
10 : 1 : 2	_	Urea	4 –36 LA	144	8	5
10 : 1 : 3	_	Urea	3 – 30 LA	144	7	5
10 : 1 : 1	$Sn(oct)_2$	Urea	3 – 20	144	12	5
12 : 1 : 1	$Sn(oct)_2$	Urea	6 – 38	144	15	4.5
12[a] : 1 : 1	$Sn(oct)_2$	Urea	6 - 28	144	12	4
12[b] : 1 : 1	$Sn(oct)_2$	Urea	6 – 34	144	15	4.5

[a] L-lactide was used rather than D,L-lactide; [b] D-lactide was used rather than D,L lactide

N/D No data as the product was insoluble in all solvents investigated.

4.4.4b. Melt Polymerisation Initiated by Urea with Stannous Octanoate Catalyst:

As an additional reaction to ascertain the nucleophilic potential a polymerisation of lactide was carried out in the presence of urea using stannous octanoate as the catalyst. The results are shown in table 4.4.4b.

Table 4.4.4b Table showing additional data concerning the use of urea as initiator in the presence of $Sn(oct)_2$ catalyst.

Ratio L : I	Catalyst	Mwt Distribution (LA units)	Separation (amu)	M_n (LA units)	Surfactant quotient
5.6 : 1	$Sn(oct)_2$	8-34 free PLA	144 + 72	18 LA	2
		6-34 Urea PLA	144 + 72		

4.5 PLA Copolymers with PEG and MeOPEG.

Polyethylene glycol (also called polyethylene oxide, depending on how it is produced) is the most common polyether industrially prepared. PEG is most commonly produced by ring opening polymerisation of ethylene oxide in the presence of water, ethylene glycol or with PEG oligomers (see figure 4.5). A basic catalyst may be employed but, as long as the initiator is sufficiently nucleophilic, the reaction should occur rapidly without catalyst due to the ring strain of the epoxide. PEG is produced and used with a wide variety of molecular weights from ~400 g mol^{-1} up to well over 1,000,000 g mol^{-1}. PEG is hydrophilic due to the hydrogen bonding ability of the polyether groups; this differs from simple ethers like diethyl ether, which are only sparingly soluble in water. The ether groups in PEG are more electronegative (and there are more of them) resulting in better H-bond acceptors. PEG is also soluble in a variety of organic solvents such as dichloromethane and benzene.

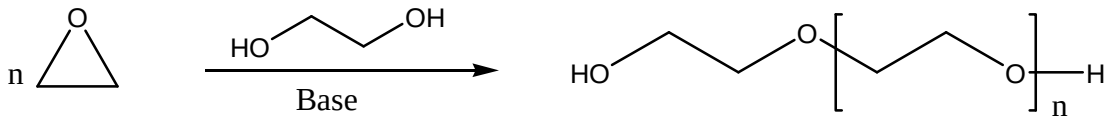

Figure 4.5. Common method of ethylene oxide polymerisation.

PEG is already present in a wide range of personal care products including toothpastes, creams, lubricants and laxatives. It also has a wide range of uses medicinally such as for whole bowel irrigation before surgery or colonoscopies. More importantly it has been used in a variety of protein-based medications to slow the retention time of the drug in the bloodstream, thus increasing the medicinal effects and dosing times.

The copolymers of PEG and PLA are being investigated as drug delivery systems; as both PLA and PEG are non-toxic polymers. The known characteristic of these polymers is that the hydrophilic PEG attached to the hydrophobic PLA leads to swelling into a gel (noted for sol-gel transitions) in water or water/organic mixtures, The swelling can be controlled thermally depending on Mwt etc.

In this project the use of PEG was somewhat limited in the scope of the investigation. Copolymers are more difficult to analyse than polymers as there is a much greater spread of molecular weights. In order to fully explore the production of copolymers a GPC is ideally required onsite. The polydispersity of the initiating polymer (PEG) should also be known as it can be used as a correction factor when deciding how much lactide to use to obtain the desired molecular weight.
As polyethylene glycol is widely used in surfactants, the copolymers produced with PLA were used for comparing the effectiveness against the other surfactants produced.

4.5.1 Analysis of PEG Containing Copolymers.

The analysis of PEG containing copolymers was difficult given the restrictions with equipment (a GPC is the most useful analysing technique for copolymers.) Mass spectrometry has its uses still, though is not a very useful method at looking at copolymers as there are always at least two sets of distribution patterns which often overlap making defining the polymer peaks difficult. In this case separation in the MALDI-TOF consists of 44 amu for PEG repeat units and 72 or 144 for PLA repeat units. MALDI-TOF spectra can range from the very clear (figure 4.5.1a) to the incredibly complicated (figure 4.5.1b). It is however useful to compare the raw spectrum of the initiating PEG with that of the copolymer to give some indication as to whether PLA is attached, though it could be considered optimistic (except in cases where the lactide ratio is high) to adequately see the polymer distribution or estimate the length of PLA chains attached to PEG. Figure 4.5.1c shows the MALDI-TOF for PEG_{1000}, which was used as initiator in figure 4.5.1b. It can be seen that there is a shift of ~ 376 amu between PEG_{1000} and the copolymer. The polydistribution of PEG should not change in the reaction and therefore it can be considered that any shift in

molecular weight is as the result of PLA on the chain. If we assume this is correct then we can say that the PLA chains are, on average, 5 LA units long.

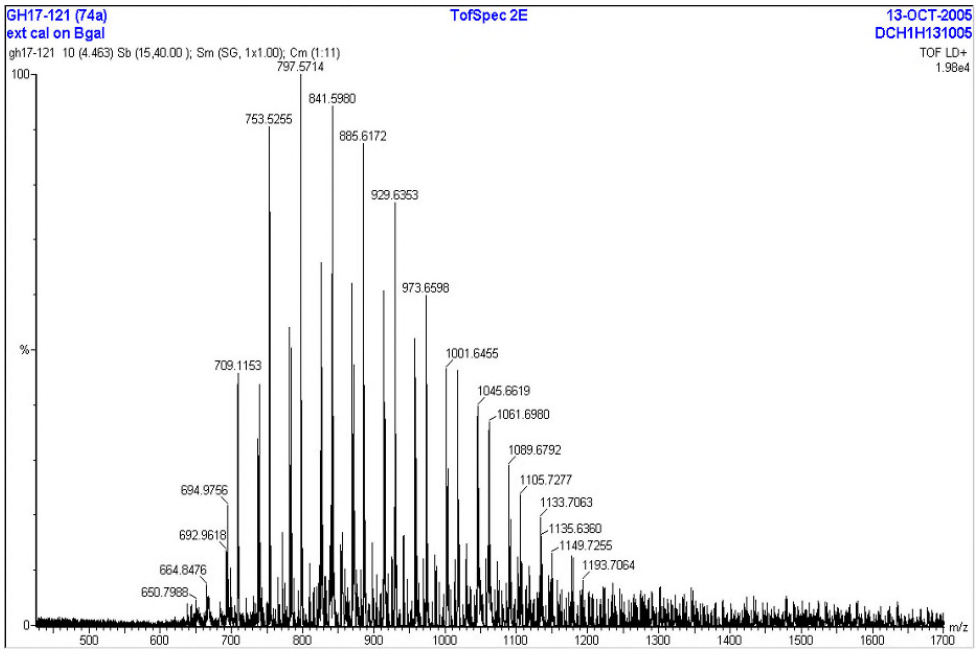

Figure 4.5.1a The MALDI-TOF spectrum of a MeOPEG copolymer. The spectrum shows only the distribution of the PEG (ratio of L : PEG was only 1 : 9)

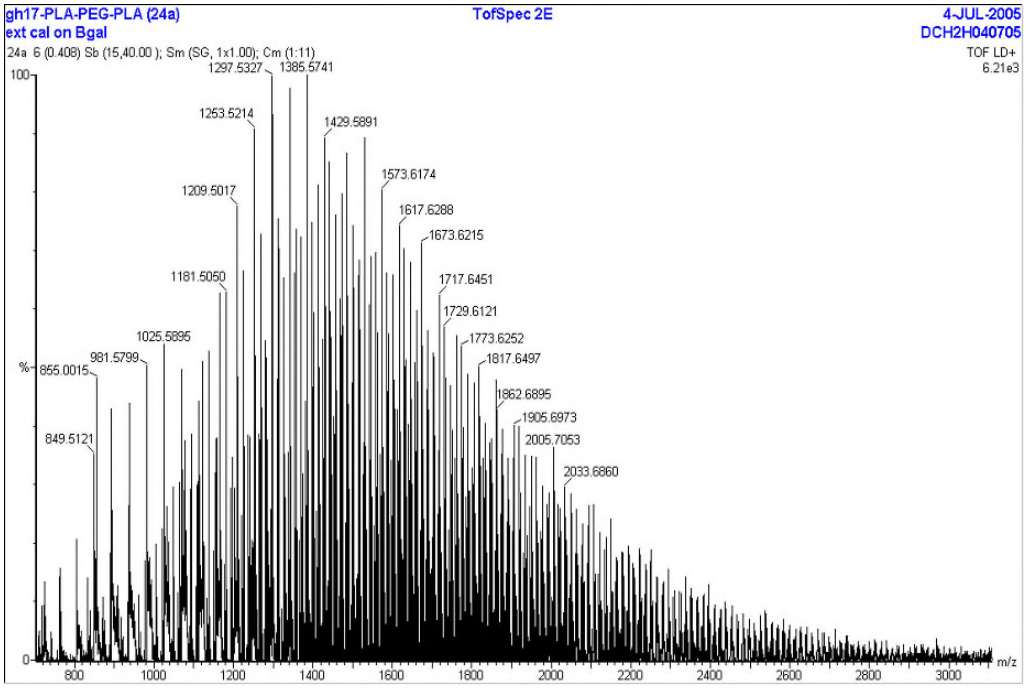

Figure 4.5.1b The MALDI-TOF spectrum here showing dense mass of peak clusters. The main peaks are again 44 amu apart, but the abundance of peaks makes peak separation measurement difficult.

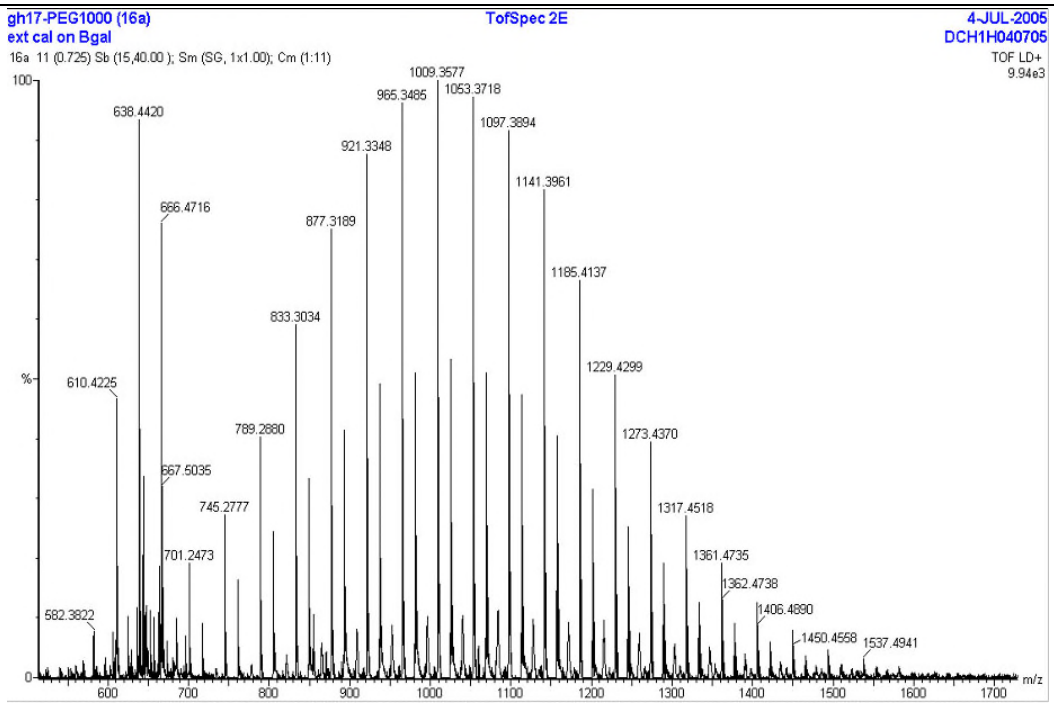

Figure 4.5.1c MALDI-TOF mass spectrum of PEG1000 purchased from Aldrich. The secondary distribution is likely due to other PEG polymers present as impurity due to whatever initiator was used.

It is more inherently difficult to analyse copolymers the shorter the PLA chains, this is also true for the end group analysis in the ^{1}H NMR spectra. Due to the fact that PEG chains are longer, but contain lower Mwt repeat units they make up a vast amount of the intensity of the NMR spectrum, making the integrals for the PLA very difficult to see, especially the end group.

4.5.2 Surfactant Ability of PEG Copolymers.

The surfactant abilities of PEG/PLA copolymers are as expected. They are low foaming and have a surface tension of 40-44 mN m^{-1} at 1 mg cm^{-3} concentration. They show relatively good solubility in water depending upon chain length. The emulsification behaviour of PEG copolymers was mixed. Only under high shear did they form thick emulsions (water/toluene), but their stability was poor. After only a few hours the emulsion had creamed, forming two separate emulsion layers (W/O and O/W). As a comparison to other surfactants mentioned in this chapter, the surface tension is quite comparable with that of the choline chloride initiated PLA and with the surfactants to be discussed in chapters 5 and 6.

MeOPEG$_{750}$PLA copolymer was tested for its emulsification behaviour using a Silverson mixer at 4000 rpm and the solution was kept cooled in ice. A 3 % by weight solution of the copolymer was prepared in toluene. It was used in a 1 : 3 ratio where the water was added slowly to the mixing solution via a syringe. Once all water was added the solution was continuously sheared for 15 minutes before being allowed to stand for a further 20 minutes. After 20 minutes the emulsion began to show signs of separation but did not separate until after 1 hour. The photographs below (figure 4.5.2) show the emulsion after 1 hour and after 1 month.

a) b)

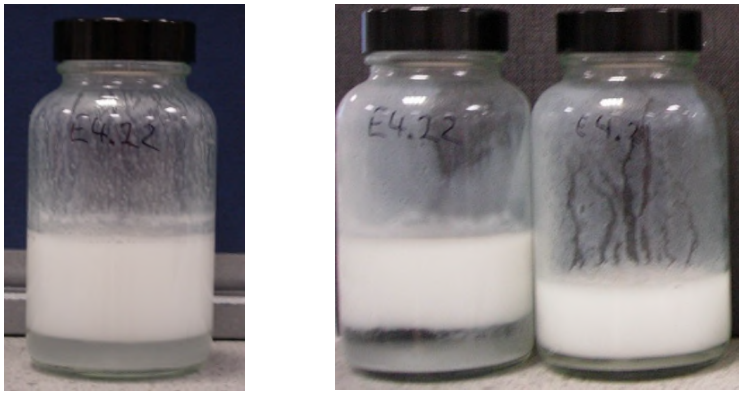

Figure 4.5.2 Shows the MeOPEGPLA water/toluene emulsion after a) 1 hour and b) 1 month.

It can be clearly seen that creaming does occur in this instance, which indicates that this copolymer is not ideally suited to this type of emulsion. From the separation it may be better to use a 2 : 1 ratio of water to toluene.

4.5.3 Ring Opening Polymerisation of Ethylene Carbonate.

During this stage of the project, there was a brief tangent to explore another method for producing random stereoblock PEG/PLA copolymers. It is possible to produce PEG by ring opening polymerisation of ethylene carbonate (see Figure 4.5.3). Some very similar reactions have been carried out using glycerol carbonate to form dendrimer and hyperbranched type systems. For this ROP a strong base is required usually potassium hydroxide or carbonate, but the presence of the strong base makes it difficult to use in conjunction with lactide, as the lactide molecule has far more ring strain and is much more easily ring opened. This system also added a further complication that PLA rapidly transesterifies, but PEG does not.

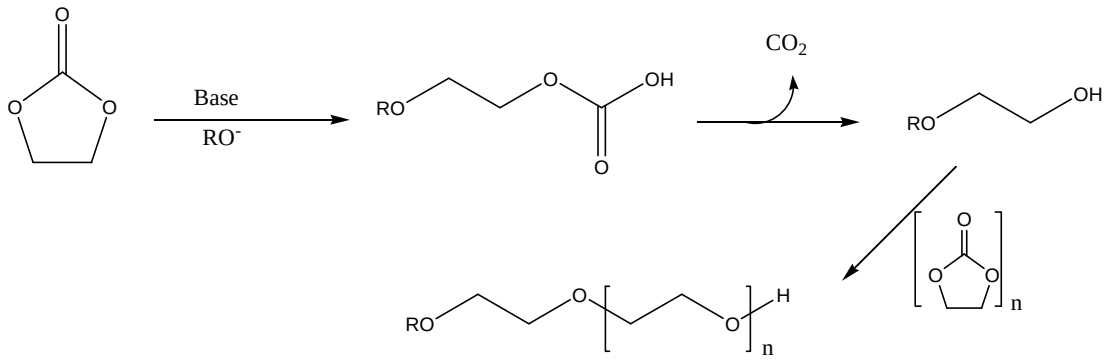

Figure 4.5.3. Simplified mechanism of ROP of ethylene carbonate.

One of the most limiting factors in this reaction is the elimination of CO_2, which only occurs rapidly if the reaction is carried out at high temperature, >150 ^{o}C. When KOH [12] has been used, there has been evidence for carbonate units in the polymer chain suggesting that even the carboxylate unit is nucleophilic enough under these circumstances to ring-open the ethylene carbonate. The reaction temperature was a limiting factor. As with lactide, polymerisation with short chains transesterification occurs rapidly at high T, and normal reaction conditions for melt polymerisation were at 130 ^{o}C, which was not high enough for ethylene carbonate polymerisation. It had been suggested in the paper by Lee *et al*. [12] that Lewis acid or base catalysts or transesterification catalysts could work when using ethylene carbonate, and certainly some polymers have been produced [13] where stannous chloride was used as catalyst. Use of more conventional lactide ROP catalysts, such as DMAP and stannous octanoate gave poor results at these reaction temperature and no PEG polymer longer than a trimer was formed. Mostly unreacted carbonate was recovered. Most important of all was that the PLA produced consisted solely of free PLA chains.

Due to the problems inherent in the reaction this seemed an unviable method, and without a GPC, there was no way to properly analyse the copolymer that would be produced so this idea was abandoned. Had it been successful, there would have been some scope perhaps to look at hyperbranched polyglycerol PLA copolymers which may be of considerable interest for emulsification (possible rheopectic emulsifier).

4.5.4 Conclusion.

After the poor results with the sugar work, and the mixed results with the choline chloride, there proved to be many difficulties in finding the ideal hydrophilic initiator for lactide polymerisation. PEG works very well at high lactide ratios, but there was a wealth of research already into PEG/PLA copolymers. In addition, PEG is not biodegradable or biorenewable, so it did not seem the ideal choice for a novel range of biodegradable surfactants and emulsifiers. Even if microbes were eventually able to degrade PEG, ethylene glycol that could be produced is toxic if ingested.

4.6 Reaction methods for producing PEG initiated PLA copolymers.

This section details the reaction methodology used for the production of PEG-PLA copolymers and the experimental results

4.6.1 Materials used for Preparing PEG Initiated Polymers of PLA

Materials:

Polyethylene glycol of M_n~ 200 to 1500 was purchased from Acros Organics or Aldrich and prior to use dried at 85 ^oC under vacuum for 3 hours.
MethoxyPEG$_{750}$ was purchased from Acros Organics and dried as described above.
Lactide was purchased from Aldrich and dried by sublimation prior to reactions.
Stannous octanoate and DMAP were purchased from Aldrich and Avocado respectively and used without further purification.

4.6.2 Experimental Methods for Producing PEG-PLA Copolymers

1) Melt Polymerisation procedure:

To a clean dry round-bottomed flask equipped with a stirrer bar, the polyethylene glycol was added and dried under vacuum for 3 h. When drying was complete the flask was heated to 130 ^{o}C and dry lactide was added in the required ratio. Once molten, the catalyst was added and the flask sealed before being submerged in the oil bath. The reaction was then left for the allotted time. When the reaction was complete the resulting copolymer was analysed by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry.

2) Solvent Polymerisation Procedure:

To a clean dry round-bottomed flask equipped with a stirrer bar, the polyethylene glycol was added and dried under vacuum for 3 h at 85 ^{o}C. When the drying of the PEG was complete, the PEG was allowed to cool to RT under vacuum before the solvent was added. To the solution dry lactide was added in the required ratio and heated to reaction temperature. When the reaction temperature was achieved the catalyst was added and a condenser fitted to the flask. The reaction was then left for the allotted time. When the reaction was complete the resulting copolymer was analysed by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF spectrometry.

Results:

Table 4.6.2 Shows the results for PLA copolymers initiated by PEG.

Expected M_n of PEG amu	PEG/PLA Ratio	Experimental Conditions	M_n of PLA (LA units)	Surfactant Quotient	Surface Tension mN/m
400 (124)	1 : 6	DCM; 45 ^{o}C; 6 hrs; DMAP	N/D	3	N/D
600 (125)	1 : 6	THF; 70 ^{o}C; 6 hrs; DMAP	N/D	3	N/D
750 [a] (118)	1 : 3	130 ^{o}C; 30 min; $Sn(oct)_2$	N/D	5	40.95
750 [a] (119)	1 : 3	130 ^{o}C; 20 min; DMAP	3	5	41.067
750 [a] (120)	1 : 6	130 ^{o}C; 30 min; $Sn(oct)_2$	6	5	43.25
750 [a] (121)	1 : 9	130 ^{o}C; 30 min; $Sn(oct)_2$	N/D	5	43.25
750 [a] (123)	1 : 20	130 ^{o}C; 30 min; $Sn(oct)_2$	N/D	4	N/D
750 [a] (B001.1)	1 : 9	130 ^{o}C; 30 min; $Sn(oct)_2$	9	3	N/D
750 [a]	1 : 20	130 ^{o}C; 30 min; $Sn(oct)_2$	38	4	40.93
750 [a]	1 : 17	130 ^{o}C; 30 min; $Sn(oct)_2$	34	4	N/D
1000 (90)	1: 6	130 ^{o}C; 30 min; $Sn(oct)_2$	10	4	40.14
1000	1 : 60	130 ^{o}C; 30 min; $Sn(oct)_2$	18	3	N/D
1000 (B10)	1 : 40	130 ^{o}C; 60 min; $Sn(oct)_2$	36	4	N/D
1500 (126)	1 : 6	130 ^{o}C; 30 min; DMAP	6	5	N/D
1500 (127)	1 : 12	130 ^{o}C; 30 min; DMAP	10	4.5	N/D
1500	1 : 30	130 ^{o}C; 90 min; $Sn(oct)_2$	58	3.5	N/D
1500 [b]	1 : 30	130 ^{o}C; 90 min; $Sn(oct)_2$	54	4	N/D
1500 [c]	1 : 30	130 ^{o}C; 90 min; $Sn(oct)_2$	54	N/D	N/D
1500	1 : 40	130 ^{o}C; 90 min; $Sn(oct)_2$	58	N/D	N/D
1500 [b]	1 : 40	130 ^{o}C; 90 min; $Sn(oct)_2$	80	3	N/D

[a] Polyethylene glycol methyl ether; [b] D-PLA; [c] L-PLA

4.7 Conclusion

It is clear from the results discussed in this chapter that poly(lactic acid) can be used successfully as a hydrophobic tail for a polymeric surfactant as long as a suitable initiator is employed such as choline chloride. The reactions with choline chloride may warrant further investigation as there is sufficient evidence to show that from a choline chloride/urea eutectic mixture these polymerisations occur without the addition of further catalyst, which could lead to new green chemistry methodologies for the production of PLA, which could be the basis of much further work.

There has already been and continues to be considerable work on PLA-PEG copolymers for sol-gel applications etc. and it does offer an attractive means of producing surface active polymers, however, the green chemistry aspects of these are considerably more speculative owing that they require a catalyst and PEG although not considered toxic is not readily biodegradable.

Any further study of sugars as initiators for ROP of lactide could perhaps be extended to include short chain polysaccharides (as they contain many hydrogen bonding sites) or cellulose derivatives as they continue in the trend of biorenewable and biodegradable materials. However, any foray into this area will likely require research into new solvent systems i.e ionic liquids, supercritical fluids and the use of highly selective catalysts such as enzymes.

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Chapter 5:

The Formation of Poly(lactic acid) Surfactants in a One-Step Process by Initiation with β-Hydroxyacid Alkali Metal Salts.

5.0 Aim

The aim of this section of my thesis was to come up with a simple idea to produce PLA's with surfactant behaviour that was both cheap and environmentally benign. It had been noted when testing the PLA alkyl esters that the addition of base to produce Na chain ends resulted in better hydrophilicity. This led to the idea that perhaps a sodium or potassium PLA chain end would in itself be hydrophilic enough on longer chain PLA to promote good surfactant behaviour. Within this chapter I will discuss:

1) Why this is an interesting development in PLA surfactant production.
2) The methods used to produce Na^+ or K^+ containing PLA chains.
3) The Mechanism of these reactions.
4) The different initiators used, why these were chosen and how they were produced.
5) The physical characteristics of these polymers.

5.1 Introduction

In previous chapters the production of PLA was focussed on initiation with either a hydrophobic initiator (long chain alcohol) or a hydrophilic initiator (sugar, PEG, choline chloride), but these types of reaction generally required the addition of a catalyst. From previous work [1] it was known that alkaline metal hydroxides and carbonates can initiate ring opening polymerisation of lactide; however, the reactions are notoriously inefficient due to transesterification side reactions etc. Kricheldorf [2] had studied the usefulness of sodium lactate and mandelate as initiators for lactide polymerisation and concluded that they were of little use because racemisation and transesterification occurred preventing high Mwt. polymers from being formed. This

however, is not a problem in producing PLA surfactants, as there is a maximum chain length of around 30 LA units before the polymer becomes fairly inert in water.

Sodium salts of fatty acids are among the simplest and most common soaps known. Sodium palmitate (C_{16}) and sodium stearate (C_{18}) are commonly found as the main constituent of bars of soap, and have been used for thousands of years. It was however, relatively unknown what effect a polyester would have in place of a carbon chain. There are several key ideas that need to be considered. For instance, the interaction between polyester chains is different from that between alkyl chains. Alkyl chains are held together by relatively weak Van der Waals forces, but polyesters, especially those with short monomer units pack electrostatically or by hydrogen bonding with bridged water, both of which are much stronger interactions.

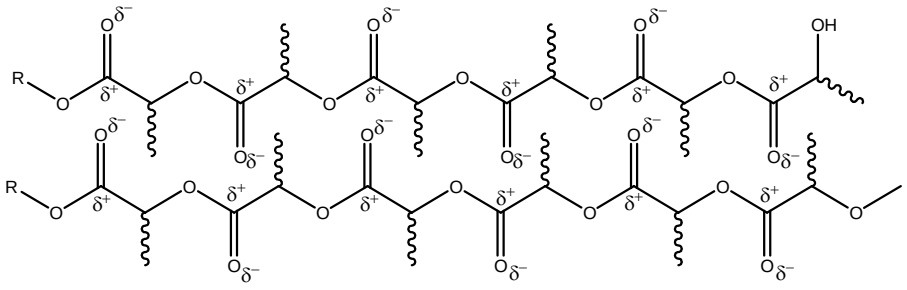


Figure 5.1.1 Showing electrostatic interactions between polymer chains.

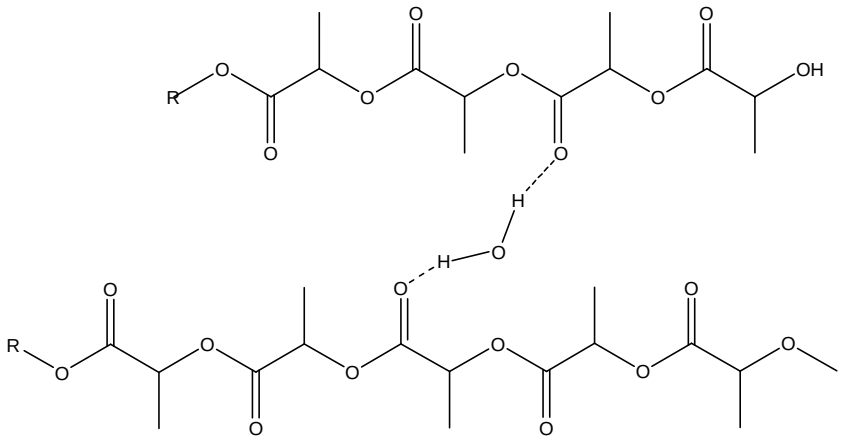
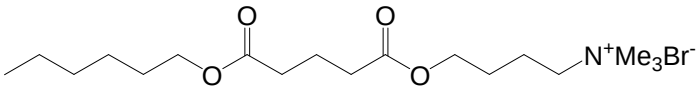
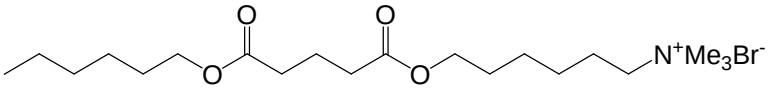
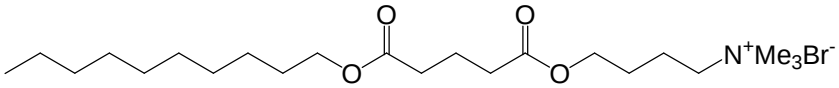
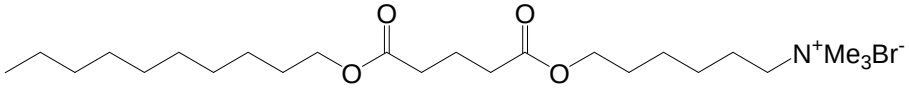
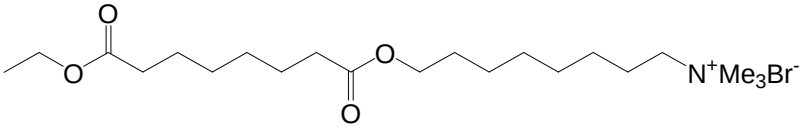
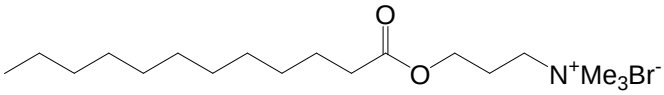
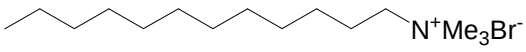
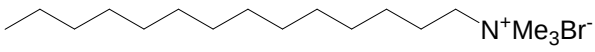


Figure 5.1.2 Showing possible hydrogen bonding interactions mediated by water.

The actual usefulness and properties of polyesters as hydrophobic chains has not been extensively studied in terms of surfactants and emulsifiers, although they have been used in producing sol-gel materials. Menger *et al*. [3] studied the effect of having one or two ester groups present in an alkyl chain of up to 20 carbon atoms in a conventional surfactant. These were compared with well-known surfactants DTAB (dodecyltrimethylammonium bromide) and TTAB (tetradecyltrimethylammonium bromide). In this instance it was discovered that the hydrophobic segments of the ester containing surfactants (segmented) had equal hydrophobic potential to alkyl chains of equal length (contiguous). What the authors noted as a major difference however, was the higher degree of aggregation leading to differences in micellar behaviour. In some cases the ester groups hindered micellization. The aggregation behaviour can be explained in terms of the longest contiguous segments of the chains. The table below shows the surfactants that were produced along with their CMC values and aggregate size.

Table 5.1.2 shows the surfactant structures and their micellar properties.

Label	CH_2 units	Structure	CMC mM	Area $Å^2$
A	12		2.4	81
B	14		2.5	123
C	16		2.2	75
D	18		1.4	75
E	15		1.0	334
F	13		4.6	54
DTAB	11		13.3	64
TTAB	13		3.3	52

It is clear that the different positions of the ester groups will lead to some differences in the packing efficiency. Structure E provides a low CMC and a high aggregation number – in this case these properties may be due to the pendant nature of the ester groups that mean that there is a higher probability of electrostatic interaction no matter how the molecules orientate themselves.

The nature of the electrostatic interactions and aggregation directly relates to the packing efficiency and micellar formation in PLA, although there are other structural factors that should also be considered with PLA, other than the pendant nature of the repeat units. Isotactic PLA is known to be helical in shape [4, 5] and can be either an α or β helix. An alpha helix is the shape we associate with DNA type molecules and a beta-helix (or beta-sheet) is a hydrogen-bonded layer of repeating polymer that looks similar to ripples or pleats (or repeating chair-type configuration).

It is these interactions that make the study of PLA as a hydrophobic group interesting as there is a very high degree of electrostatic interaction. This would suggest that PLA will give very low CMC values, aggregate very easily and form large aggregates. The polymers should also easily swell if water can penetrate and these swollen aggregates may have some uses, in terms of transport media (vesicles, capsules) for drug delivery. What needs to be determined is whether these interactions make these initiators suitable for use as emulsifiers.

Emulsions can be thought of as arising from strong interactions of micelles produced by the mixing of two immiscible phases in the presence of an emulsifying surfactant. The type and shape of the surfactant is critical to the behaviour of the surfactant as is the solubility of the surfactant in the different layers. Emulsions between water and organics are the simplest to explore. PLA has a hydrophobicity that is tailorable by chain length, and depending on the organic phase, a surfactant may be produced, which is more soluble in one phase than the other.

5.2 Beginning with Sodium Lactate

Sodium lactate is a white powder that smells like off milk and has a variety of uses in foodstuffs. It is a cheap and readily available starting material that has a good solubility in molten lactide. It was chosen primarily for its availability and for the fact that it would be a simple system to analyse both by NMR spectroscopy and MALDI-TOF spectrometry methods.

5.2.1 Sodium Lactate Mechanism

Sodium lactate was already established as a catalyst initiator for lactide polymerisation in a little known work by Kricheldorf *et al*. [2]. The authors cited it as a poor initiator for lactide polymerisation, as it shares the handicaps observed when base is used as the initiator. For this reason it was important to establish what mechanism was actually at play in lactide polymerisation initiated by sodium lactate. The mechanism I had hypothesised was that there was tautomerisation (1) between the sodium carboxylate and sodium alkoxide on the lactate molecule, or at least the formation of alkoxide from neighbouring carboxylate groups and to assess whether this was the correct mechanism a series of experiments was carried out to ascertain what was occurring. The following equations illustrate the formation of the active initiators during ROP when these conditions were employed:

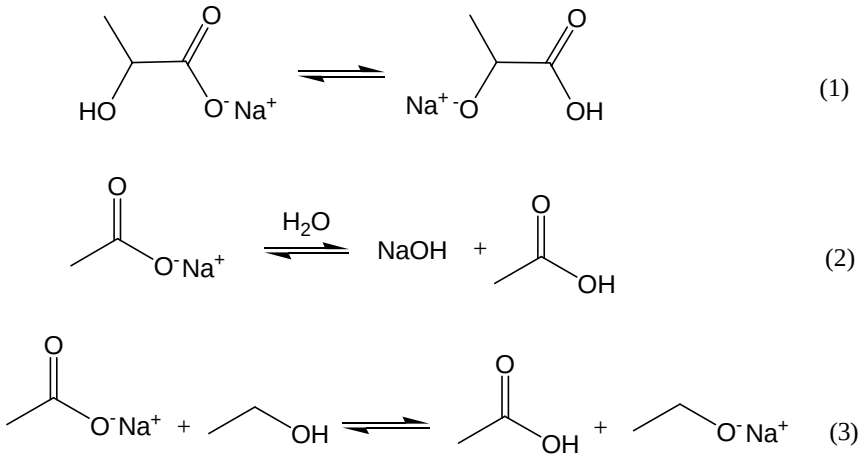


Figure 5.2.1 Chemical equations illustrating what could be occurring in the Sodium lactate tautomerisation mechanism.

Equation 2 represents two experiments that were carried out using different sodium carboxylate precursors, water is often present in lactide polymerisation in trace amounts, and may be formed if a condensation reaction occurs. In one experiment sodium acetate was used, but had poor solubility in molten lactide and so another with sodium stearate was also carried out. Both reactions yielded a small amount of PLA, and none of the polymer produced had any of the carboxylate attached.

Equation 3 represents a reaction where ethanol was used in conjunction with sodium acetate (improved sodium acetate solubility), the result was a polymer that contained the ethoxide group at one end, showed better conversion of lactide and a much longer polymer. This confirmed, along with MALDI-TOF evidence, that sodium lactate reacted through the alkoxide to form PLA sodium salts, and so could be used as both catalyst and initiator for short chain PLA molecules.

The MALDI-TOF data for the sodium lactate initiated reaction confirms the uptake of the sodium lactate into the molecule. In the spectrum below (figure 5.2.1) there is a separation of 144 amu (2 LA units), but the main peaks are odd numbers of LA units rather than even.

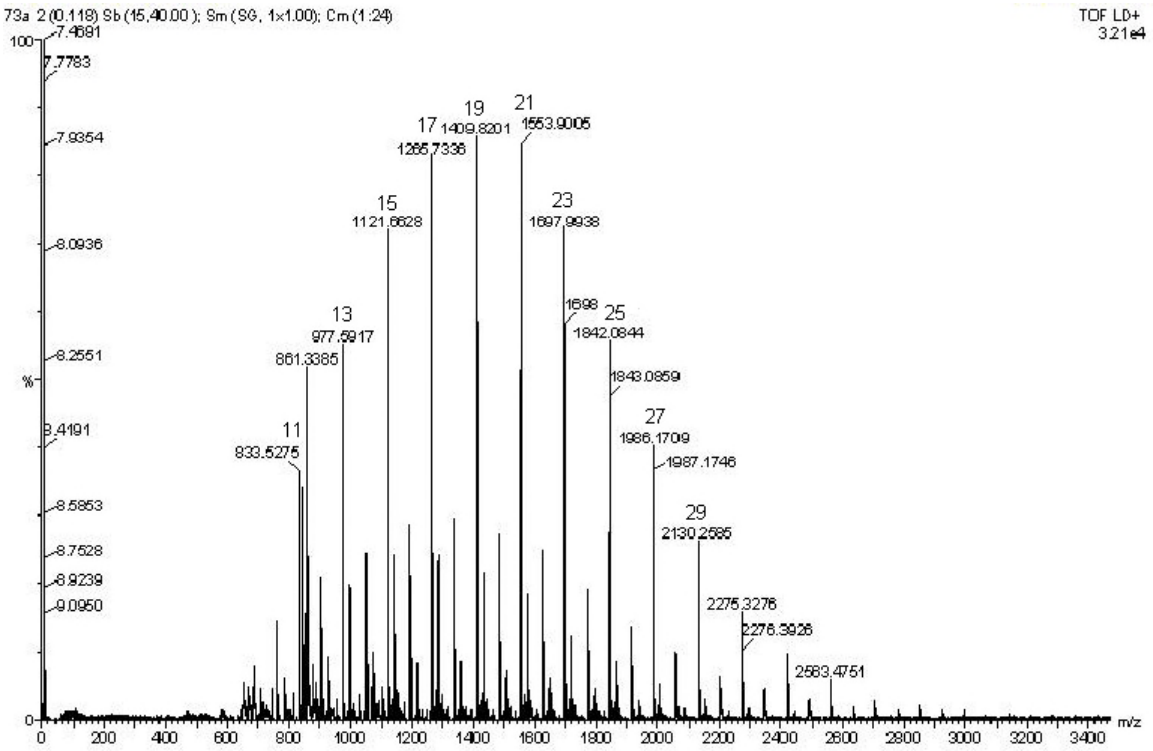


Figure 5.2.1 shows the Gaussian distribution for PLA initiated by sodium lactate where the odd numbered units are the main products.

5.2.2 Sodium Lactate Polymers

One of the most important aspects of these polymers is the relative ease by which they are made. There are upper limits to where the method can go in regards to chain length, as the reaction times cannot be over extended, because this would lead to transesterification and chain transfer – which in the case of sodium lactate can only be monitored by looking at the difference in the intensities of the odd and even repeat units in the MALDI-TOF. However, the M_n values are reasonably predictable for these polymers based upon the ^1H NMR spectroscopy and starting ratios, which is good. What is also good is that compared with the choline chloride reactions, these require no solvents or co-catalysts to be added to produce the desired polymer. There are even good results from producing these polymers in small bulk reactions >20 g.

From the results (section 5.2.3) it is clear that sodium lactate polymers have proved to have surfactant activity and show predictable chain lengths, molecular weights etc. The polymers are usually hard and transparent and are easily ground into powders making them simple to work with. What was most surprising about these polymers was that they displayed very good surfactant properties even when considering the simple nature of the polymers. Salts such as sodium stearate and sodium palmitate are well known examples of soaps, but polyester sodium salts are all but unheard of for use as surfactants. In chapter 6 more will be discussed about the solution phase behaviour of PLA salts.

5.2.3 Sodium Lactate Initiated Polymerisation

Materials:

Sodium lactate was provided by Purac and prior to use was finely ground and stored *in vacuo* over phosphorus pentoxide.

D,L and L-lactide were purchased from Aldrich and sublimed at 120 ^oC prior to use.

D lactide was provided by Purac and sublimed prior to use.

Sodium acetate was purchased from Aldrich and used without further purification

Sodium Stearate (BDH) was stored over phosphorus pentoxide prior to use.

Reaction method:

To a clean dry round bottomed flask fitted with sublimation cold finger and side arm adaptor, lactide was added and under reduced pressure was heated to 120 ^{o}C for D,L-lactide and 115 ^{o}C for either D or L-lactide for 3 hours. When sublimation was complete any lactide was scraped from the cold finger back into the flask and the flask was stoppered, before being completely submerged in the oil bath for 10 minutes at 130 ^{o}C. Once molten, a stirrer bar and sodium lactate (acetate or stearate) were added in a controlled ratio. For sodium acetate and ethanol, the ethanol was added prior to the sodium acetate. The reaction was allowed to proceed for between 20 minutes and 1 hour.

When the reaction was complete, samples were taken for NMR and MALDI-TOF analysis. The hot polymer was then poured into a cold mortar and ground to a powder on setting. The powder was then used for all further analysis (to be discussed in chapter 6.)

Results:

Sodium acetate initiated:

Lactide to initiator ratio: 6 : 1

Resulted in No PLA as the sodium acetate was insoluble in molten lactide.

Sodium stearate initiated:

Lactide to initiator ratio: 6 : 1

^{1}H NMR: M_n = 27 very higher than expected for 6 : 1 ratio, suggests reaction occurred through NaOH, rather than stearate.

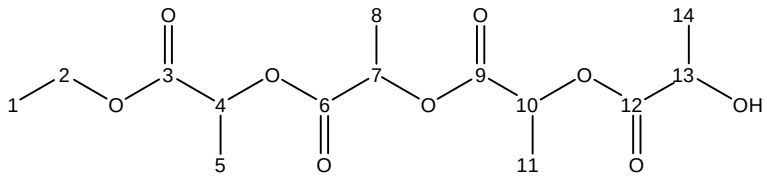
^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 15.81(CH_3, lactide), 16.64, 16.74 and 17.61(CH(**C**H_3)O, PLA), 20.51(CH(**C**H_3)OH, PLA end group), 29.69(CH_2, stearate), 69, 69.18 and 69.42(**C**H(CH_3)O, repeat unit methine), 72.47(lactide), 72.89(lactoyl lactate), 169.37 and 169.61(C=O)

The MALDI-TOF data indicates free NaPLA, with no incorporation of stearate. This suggests that polymerisation was caused by either the formation of hydroxide in the reaction due to the presence of any water, or by small amounts of lactoyl lactate (ring opened lactide, PLA dimer). Either or both could have played the part. The M_n value from end group analysis is high and not consistent with the ratio of sodium stearate used. A further attempt was made using sodium 12-HSA (which was fresher), but this resulted in poor conversion to polymer. This suggests the following conclusions; the first is that sodium carboxylates, if suitably dry, are insufficient alone for lactide polymersiation. The second point is that the distance of the hydroxyl group from the carboxylate group is of paramount importance for the formation of active initiator.

Sodium acetate : ethanol initiated:

Lactide to initiator to catalyst ratio: 6 : 2 : 1

^{1}H NMR: M_n = 8-9 lactic acid units. From NMR integral ratios all polymer contains ethoxide group. PLA methine : ethoxide 1H : 2H – 1 : 1 ratio.



^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 14.05(CH_3, C-1), 15.79(CH_3, lactide), 16.65 and 16.74(CH_3, C-5,8,11), 20.04(CH_3, acetate), 20.5(CH_3, C-14), 53.44(CH_2OH, ethanol), 61.54(CH_2O, C-2), 66.69($CH(CH_3)OH$, C-13), 69, 69.18, 69.32 and 69.42($CH(CH_3)O$, C-4,7,10), 72.46(lactide), 169.36 and 169.61(C=O).

MALDI-TOF confirms the NMR studies, showing good polydistribution ranging from 2LA units to well over 40 LA units with 72 amu separation indicating transesterification has occurred. This illustrates how potent a catalyst sodium carboxylates can be in the presence of alcohol.

Sodium Lactate Initiated

The table gives details of the ratio L : I, the reaction time, the number average molecular weight M_n determined by ^1H NMR spectroscopy, the surfactant quotient which is assigned on observations in water at 1 mg cm^{-3}; where 5 indicates high foaming and good water solubility, and surface tension determined using a Nima ST9000 manual tensiometer using the Wilhelmy plate method, taken at a concentration of 1mg cm^{-3}.

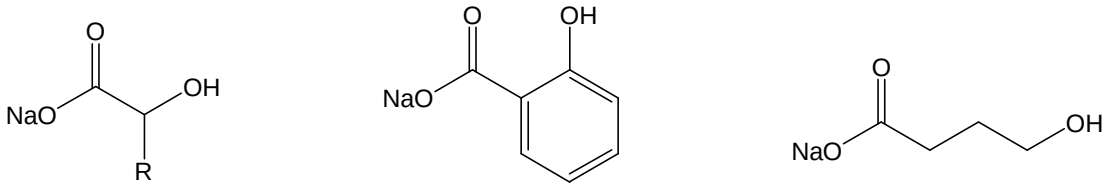
Table 5.2.2. Results for sodium lactate initiated polymers.

Ratio L : I	Reaction Time	M_n (LA's)	MALDI-TOF distribution	Surfactant Quotient	Surface Tension (mN/m)
6 : 1 [a]	25 mins	15	144	5	_
3 : 1 [a]	25 mins	Init insol.	_	_	_
12 : 1 [a]	40 mins	21	144	4	45.55
6 : 1 [b]	30 mins	12	144	4	_
12 : 1 [b]	40 mins	16	144	5	_
20 : 1 [b]	45 mins	26	144	3	_
12 : 1 [a]*	60 mins	24	144	4	_
12 : 1 [a]*	90 mins	26	144	4	_
12 : 1 [b]*	90 mins	25	144	5	48.4
6 : 1 [a]*	45 mins	13	144	5	43.55
6 : 1 [b]*	45 mins	13	144	5	49.77

[a] D,L-Lactide was used; [b] L-lactide was used; [c] D-lactide was used; * Scaled reaction >15g.

5.3 Other Naturally Occurring α, β and γ-Hydroxyacids as Initiators

The sodium salts of hydroxy-carboxylic acids can vary greatly depending on the position of the hydroxyl group relative to the carboxylate. Now that the tautomerisation mechanism has been established as the most logical route by which sodium lactate acts as the initiator for lactide polymerisation, each of these types of acid would be expected to show a different reactivity from each other in regards to initiation. Figure 5.3 shows different types of hydroxyacids.



α-hydroxyacid
lactic acid, glycolic acid
mandelic acid etc...

β-hydroxyacid
Sodium Salicylate

γ-hydroxyacid
γ-hydroxybutyrate

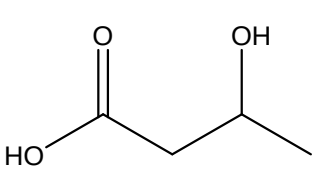
Figure 5.3. The sodium salts of the three main types of common hydroxyacids.

Many hydroxyacids occur naturally as fermentation products or metabolites. For instance lactic acid is produced from sugars by Lactobacillus bacteria, glycolic acid is found in sugar containing plants; salicylic acid is found in willow bark and is a precursor to aspirin; γ-hydroxybutyric acid (GHB) is a naturally occurring substance found in the central nervous system, beef and citrus fruits and was once used as a sedative or anaesthetic. Although now illegal in the UK it has found widespread use as a recreational drug.

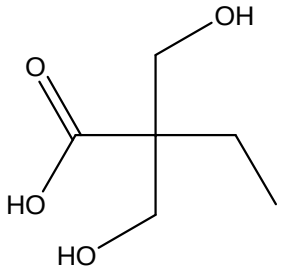
5.3.1 β-hydroxyacids as initiators

Sodium salicylate proved to be of little use in lactide polymerisation as it was not soluble in molten lactide and therefore no meaningful results could be obtained. In retrospect 3-hydroxybutyric acid, a common precursor for a variety of biodegradable plastics would have been a good initiator to try by was not at hand during this stage of the research.

A very good β-hydroxyacid salt (cheap though not naturally occurring) that resulted in interesting polymers in terms of physical characteristics, surfactant and emulsification behaviour was the sodium salt of 2,2-bishydroxymethylbutyric acid (figure 5.3.1b).



3-hydroxybutyric acid



2,2-bishydroxymethylbutyric acid

Figure 5.3.1a. Common β-hydroxyacid monomer units in polymer synthesis.

The resulting polymer is different in structure in that it follows an A-B-A block structure with the hydrophile in the middle. NMR spectroscopy confirms that reaction takes place on both arms though not necessarily evenly. Even at low lactide to initiator ratios the polymers produced are very hard and easily ground into powder. They show good surfactant behaviour and interesting emulsion behaviour (to be discussed in Chapter 6).

What is also interesting from the theoretical perspective about the polymer is the possible ways it could orient itself in solution. If we consider free rotation at the OH groups then the polymer can choose to orient itself in several different ways. It could orient itself to maximise hydrophobic interactions by covering the polar head, or it can orient itself away from the polar head or any random position in between. This structure may form vesicles (multi-core micellar systems).

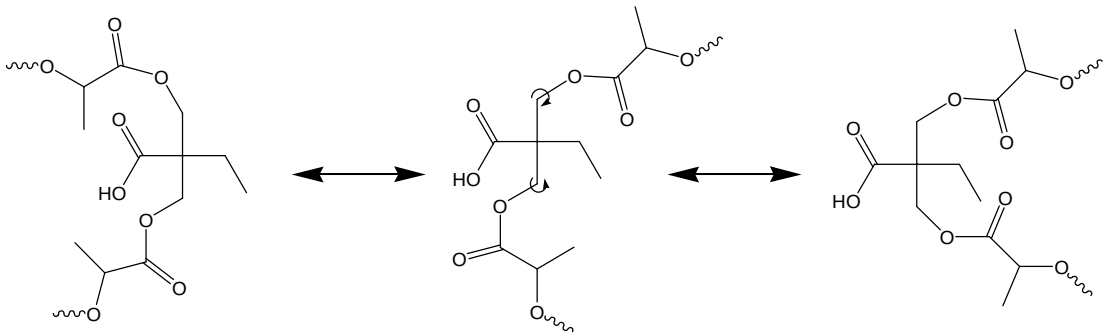


Figure 5.3.1b. The structure of NaBHB initiated PLA showing reorientation of molecule depending on environment.

5.3.2 Initiation with γ-Hydroxyacids

Some polymerisation results were obtained using sodium GHB as an initiator. These polymers were amber in colour and showed varying degrees of transesterification. In most cases this initiator worked as well as sodium lactate. In some ways it worked better. These reactions had shorter reaction times; at 130 ^{o}C the reaction was complete in 10 mins, with very little transesterification (figure 5.3.2) and good conversion. The physical properties were also slightly different; the GHB-initiated polymer was more hydrophilic but also softer and less able to be ground into a powder. One of the other major differences noted, was in the emulsion behaviour between sodium lactate and GHB initiated polymers. Sodium lactate initiated polymers produced much more stable emulsions than GHB counterparts.

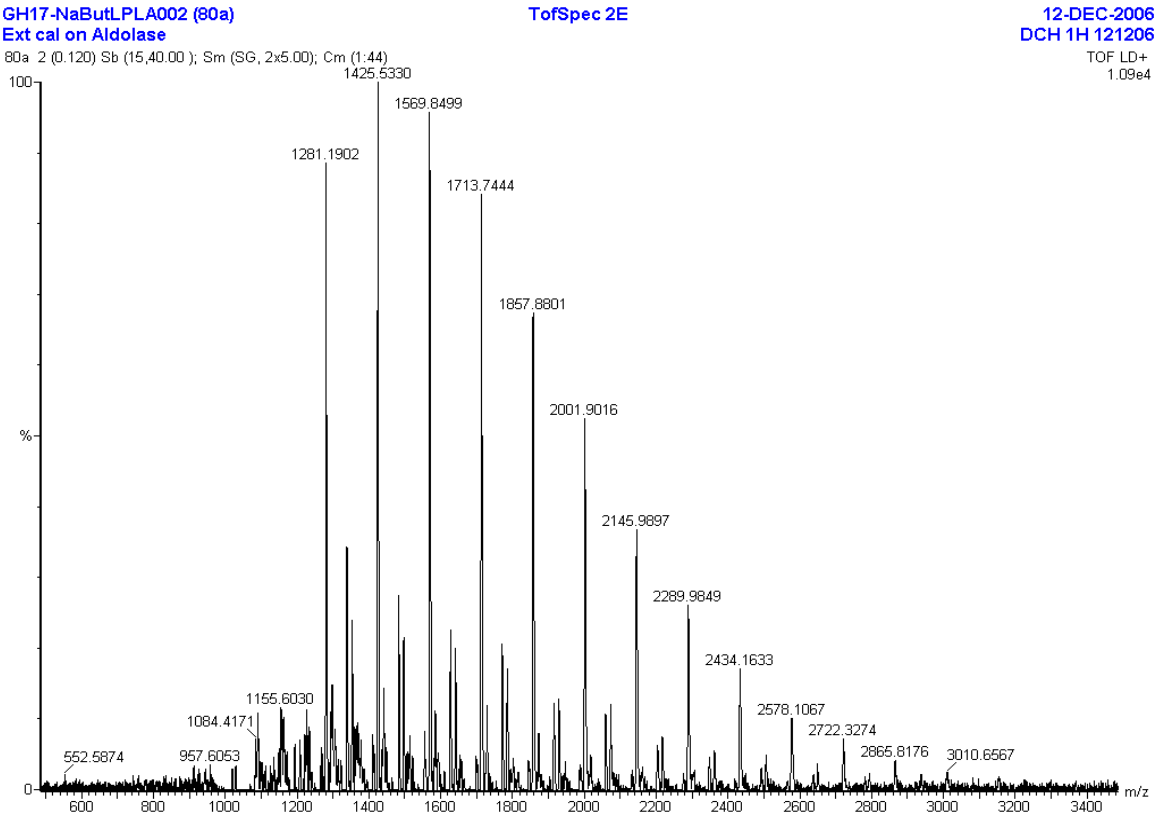


Figure 5.3.2. MALDI-TOF spectrum of g-hydroxybutyric acid initiated PLA (12 : 1 ratio, 10 mins @ 130 ^{o}C)

The reasons for the rate improvement with GHB could be related to the tautomerisation mechanism itself or to the relative nucleophilicity of the alkoxide. If we first regard the pK_a values for hydroxyacids, GHB is less acidic than glycolic or

lactic acid. The acidity here is a product of the acidity of both the carboxylic acid and the alcohol and also relates to how easily the alcohol can be deprotonated. The sodium alkoxide of the GHB is more readily formed due to GHB being a weaker acid; the acidity of the hydroxide is sufficient that it is easily deprotonated forming a more stable and reactive alkoxide.

The structures of these molecules are the most important influences on the tautomerisation mechanism. Some intermolecular cation transfer is always going to occur, but it is probably the intramolecular tautomerisation that is most important for lactide polymerisation. The reason for the increase in rate with sodium GHB is probably due to the reaction being a more irreversible transition due to a) molecular reorientation and b) the strength of the acid. A strong acid drives the equilibrium more to the LHS, but the weaker acid on GHB does not. The intramolecular reaction could be envisioned to proceed through a seven-membered transition state (figure 5.3.2b)

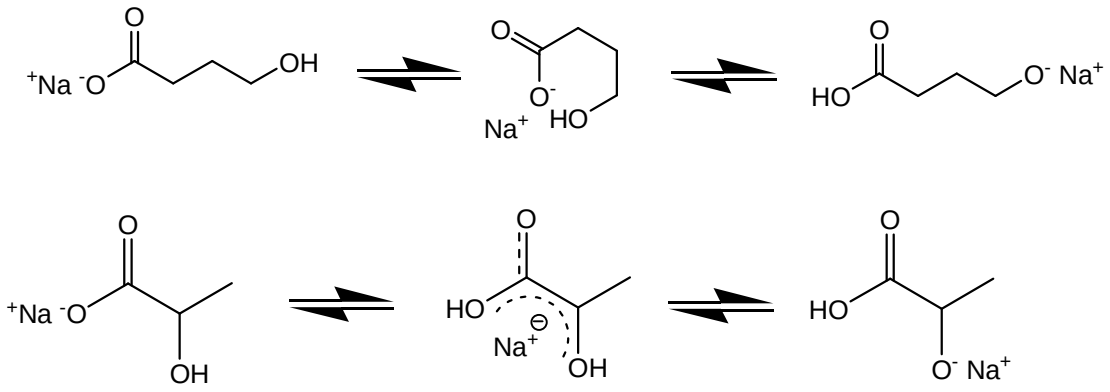


Figure 5.3.2b Intramolecular tautomerisation of Sodium GHB and Sodium Lactate.

For sodium lactate and the other α-hydroxyacids the tautomerisation mechanism probably proceeds through intramolecular relocation of the anion which is completely reversible, once the active alkoxide has formed and ring opened a lactide molecule the PLA chain carries the charge and the reaction propagates from there.

A comparison of pK_a values is shown in table 5.3.1 for various α, and γ hydroxyacids, which gives some indication of the relative acidity of the molecules as a whole, and may shed some insight as to the stability of the alkoxide.

Table 5.3.2 pKa values of common initiators [6].

Initiator	Acetic acid	Glycolic acid	GHB	Lactic acid	Malic acid	Mandelic acid	Stearic acid
pK_a (25 °C)	4.75	3.83	4.72	3.08	3.4	3.85	5.0

There is a limiting factor to using γ-hydroxyacids or other 1° hydroxyacids as initiators. There are not many of these compounds readily available. The simplest of the series, GHB will never be allowed for use in any commercial synthesis as it is a controlled substance. In a recent news article, an Australian toy manufacturer had to recall its most popular toy Bindeez™ as, by mistake, they had used 1,4-butanediol (metabolises to GHB in the body) as the plasticizer instead of 1,5-pentanediol.

γ-Hydroxypentanoic acid can be purchased as the lactone (γ-valerolactone) and could be ring opened with hydroxide in water, but there are few higher analogues available. Other primary hydroxy-carboxylic acids are known. ε-Caprolactone can be converted to 6-hydroxyhexanoic acid, 12-hydroxylauric acid can be purchased (expensive), but at this chain length tautomerisation does not occur, cation transfer is slow and very little lactide is converted.

5.3.3 Natural α-Hydroxyacids

There are many examples of naturally occurring α-hydroxyacids, though not all of them are useful in lactide polymerisation. Citric acid, tartaric acid and malic acid although they can form eutectic mixtures have little or no solubility in molten lactide especially in their salt forms. Polymers arising from these initiators would have been interesting with regard to polymer shape for surfactant and emulsification behaviour.

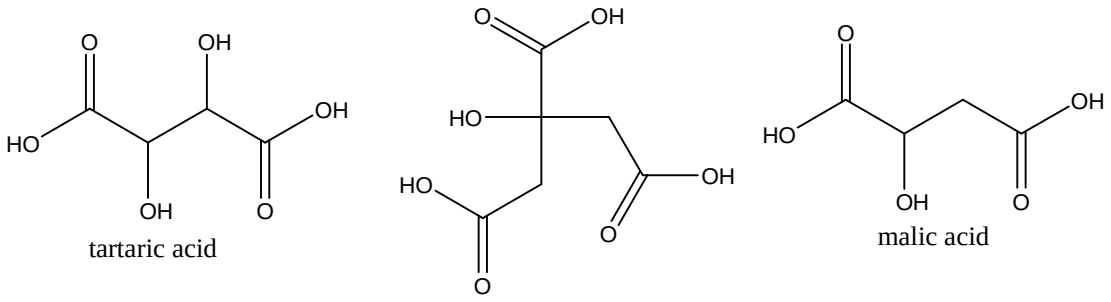


Figure 5.3.2a. Some of the common naturally occurring α-hydroxyacids.

There is one other naturally occurring and readily abundant α-hydroxyacid that has shown some interesting polymer behaviour in terms of structure, surfactant and emulsification behaviour. Mandelic acid (figure 5.3.3b) is a hydroxyacid, found naturally in almond extracts and is naturally produced in the body in small amounts from adrenaline metabolism. Like all mid-chain hydroxyacids it has a stereogenic centre on the C atom α to the hydroxide and the D,L and L forms are readily available. Poly(mandelic acid) is a biodegradable polymer that has properties similar to polystyrene and will probably find a great deal of future use. Like PLA it can be produced directly from condensation polymerisation or from ROP of mandelide (the cyclic anhydride).

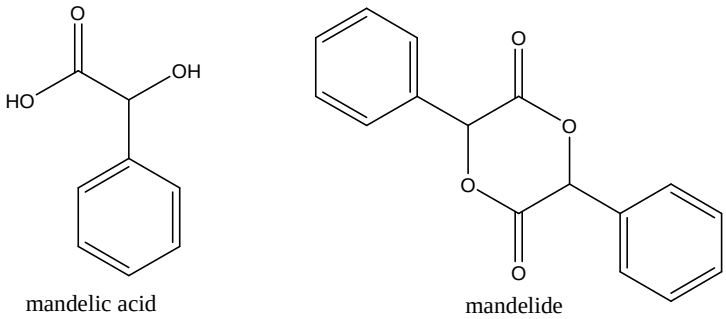
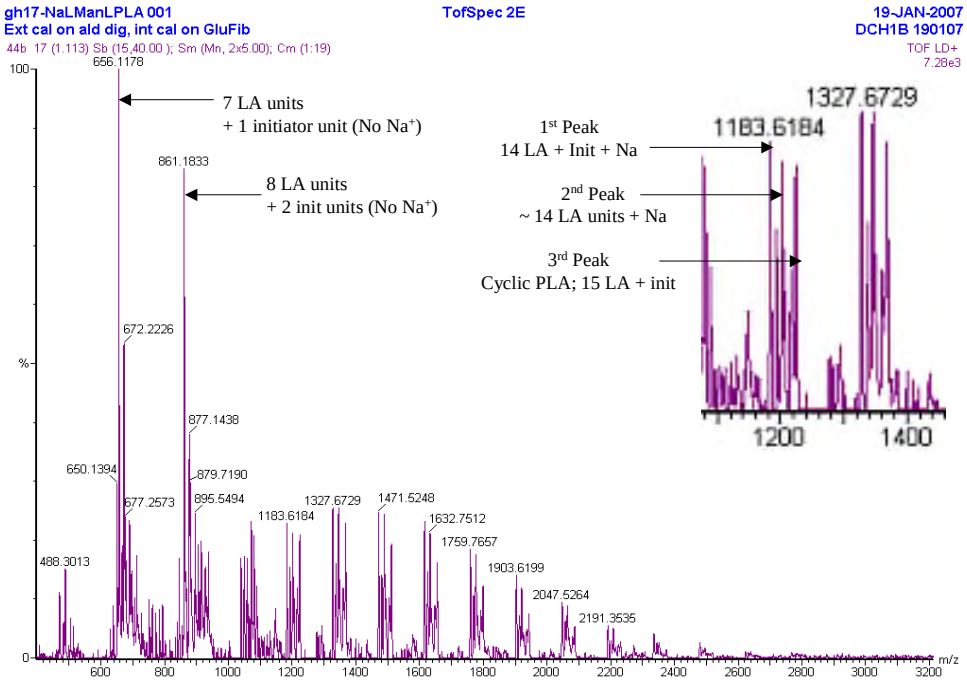


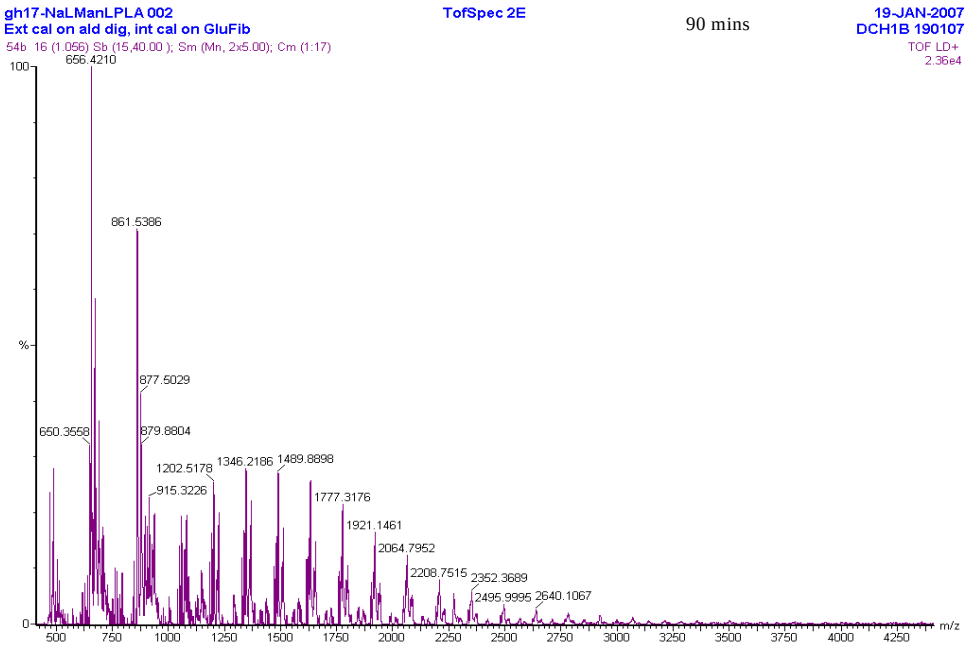
Figure 5.3.3b. Structure of mandelic acid and mandelide.

Sodium mandelate was an interesting initiator for lactide polymerisation. In some instances it was involved in an unusual secondary reaction mechanism, which was responsible for up to 3 mandelic acid units being incorporated into the polymer chain. A study on the transesterification behaviour (spectra a-f) of mandelic acid revealed that as time goes on the transesterification favours free PLA (which was expected) but it was easy to see this as it happened. However, the peaks at 656 and

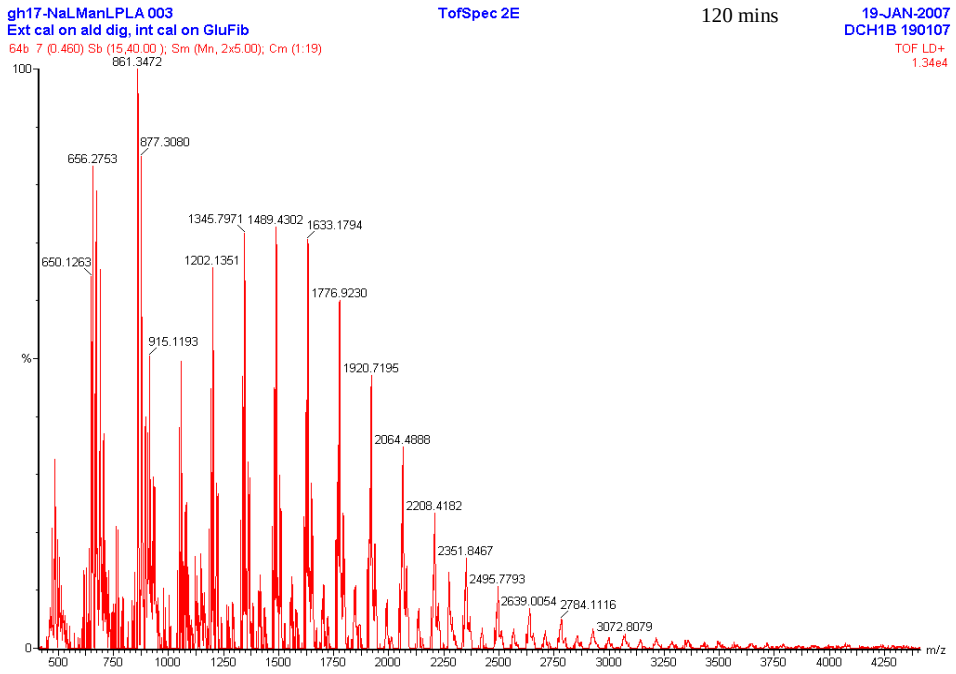
861 (2 init + 9 LA units) remain strong throughout the series. The M_n value (determined by ^{1}H NMR spectroscopy) however only fluctuates by 1 unit between spectrum a) and spectrum f).



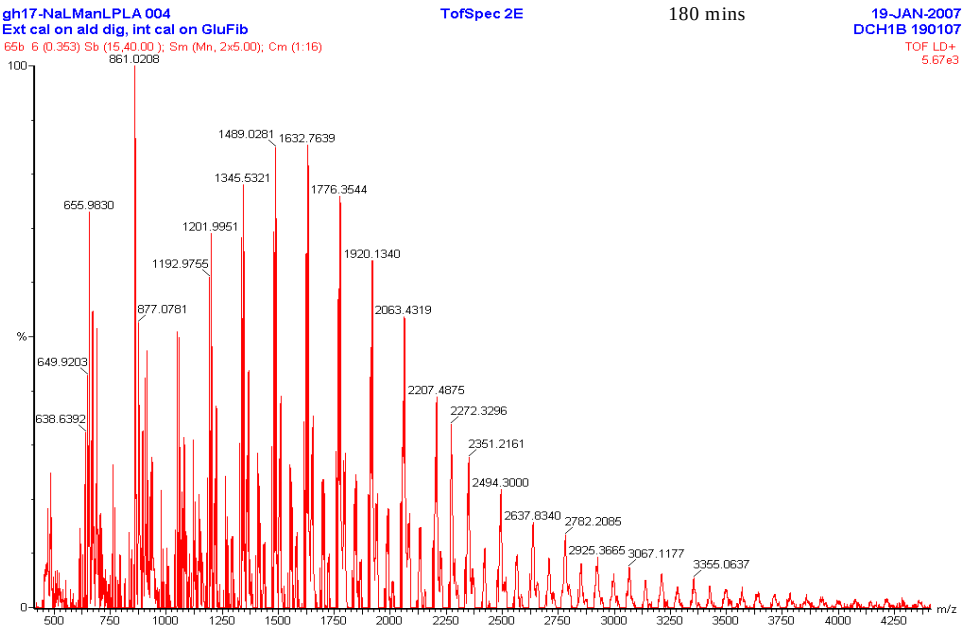
Spectrum a: Reaction after 60 mins. 861 amu = 2 init + 8 LA units. 2nd peak is 16 amu from 1st peak, 3rd peak is 18 amu from 2nd peak, 34 amu from 1st peak.



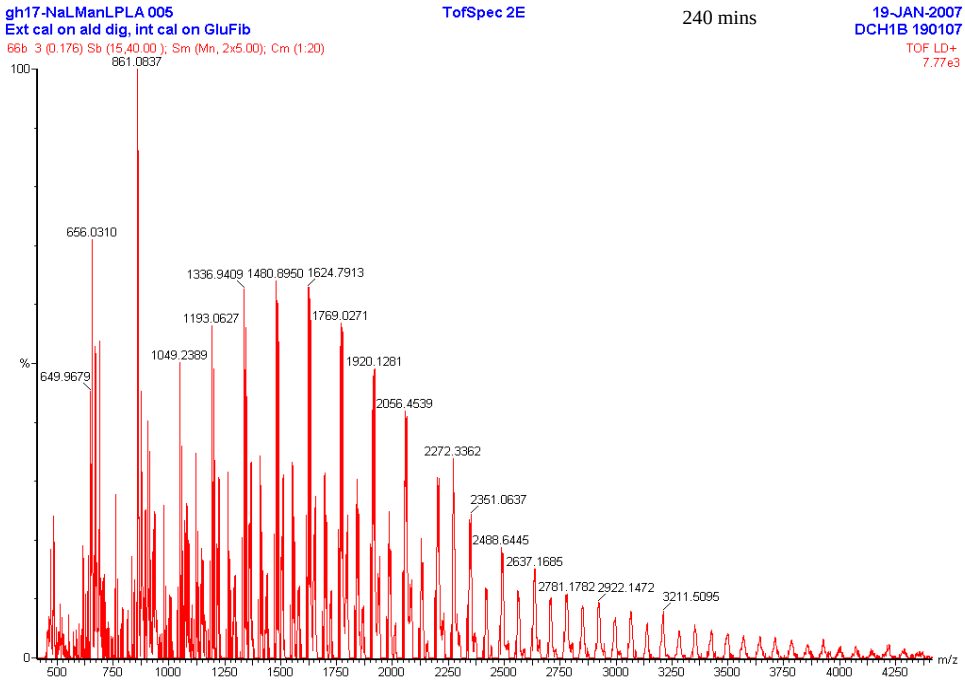
Spectrum b: After 90 mins. Slight change in mass along the spectrum, retains 144 separation



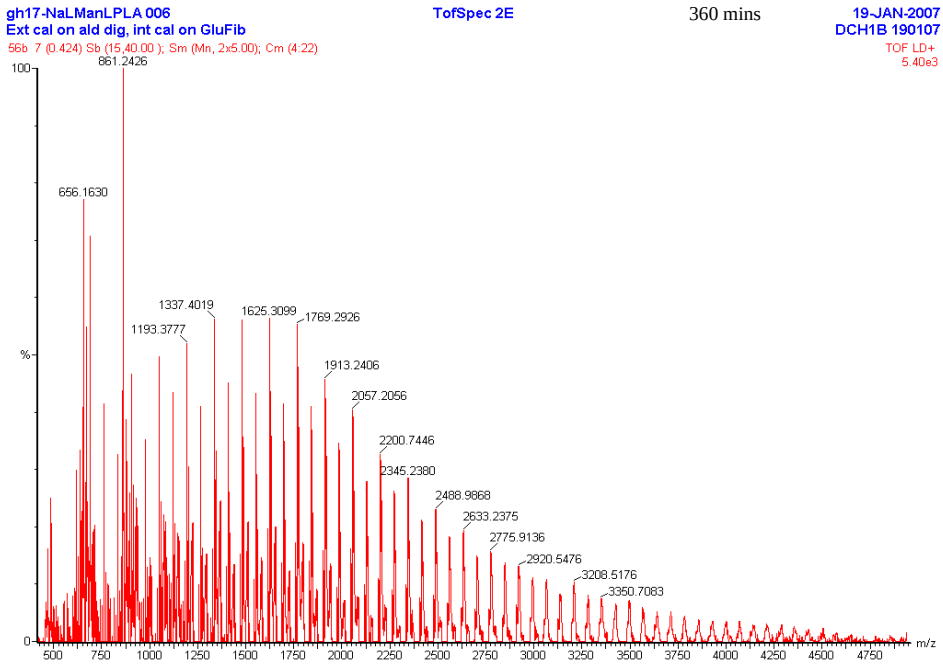
Spectrum c: After 120 mins. Peaks at 1345 are off by 10 for free PLA, and do not fit other peak sets. They vary by +18 amu from spectrum a).



Spectrum d: 180 mins. Showing change as more free PLA is being produced.



Spectrum e: 240 mins. Mostly free PLA due to rise in transesterification.



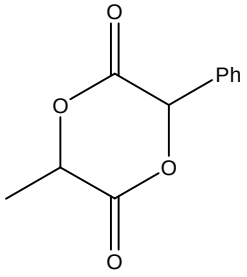
Spectrum f: 360 minutes. Shows mostly free PLA from transesterification and rise in separation of 72 amu. Peak at 1337 amu corresponds to 18 LA units.

It is clear from the MALDI-TOF data that the mechanism at play is more complicated than simply tautomerisation followed by ROP. There are three aspects that must be considered, 1) the peaks at 656 and 861 amu throughout the series; 2)

the clusters of three peaks and 3) the emergence of sodium PLA (no mandelate) later in the reaction.

1) The peak at 861 amu, which is very intense compared with other peaks in the MALDI-TOF mass spectrum appears to correspond to a polymer containing two mandelate + 8 LA units (no Na^+) (860), it is not understood why these peaks are not sodium salts! This polymer could possibly be formed by the creation of a new cyclic dimer formed from lactic acid and mandelic acid (figure 5.3.3c) and incorporation of this into the growing chain. The observation of an **even** number of LA units in this molecule is not, however, consistent with simple initiation by mandelate and incorporation of a mixed dimer, since this should give an **odd** number of LA units in the chain. One possible way in which an even number of LA units could occur in the chain initiated by mandelate and containing a second mandelate moiety would be if the mixed dimer were formed from the selective reaction of free mandelate with the end group of the growing chain to give the dimer and a chain with an odd number of LA units. This new chain (mandelate initiated with 7 LA units, 656 amu) is observed in the MALDI-TOF mass spectrum (206 amu (corresponding to the hybrid dimer) less than 861 amu). Reaction of this polymer with the formed mixed dimer would then give the observed polymer with Mwt. = 861 amu. Why these two products are mainly observed predominately with 7 and 8 LA units respectively is not obvious.

The formation of the mixed cylic compound from sodium mandelate and a lactate unit of the growing chain also leads to the formation of sodium hydroxide. This then can become an initiator for PLA formation, which occurs later in the reaction. There are two possible mechanisms to produce the cyclic dimer (Figure 5.3.3c), an intermolecular ring closing (figure 5.3.3d a) or an intramolecular ring closing (Figure 5.3.3d b) reaction must occur.



= 206 amu

Figure 5.3.3c. Cyclic dimer formed between lactic acid and mandelic acid.

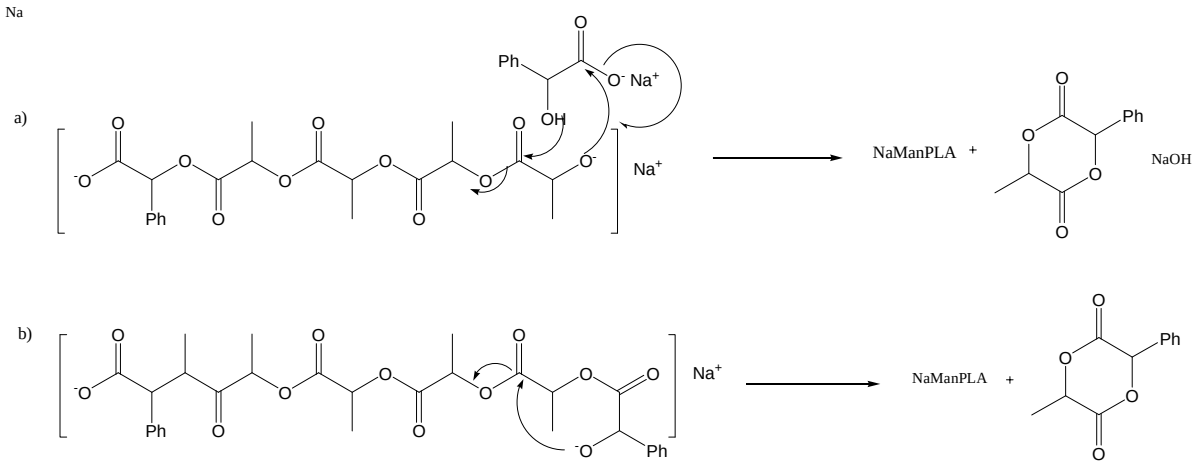


Figure 5.3.3d: Mechanisms showing how a mandelic acid/lactic acid dimer could be produced.

Mechanism b) is similar to the ring-closing depolymerisation mechanism suggested for the production of lactide, however, mechanism b) is only viable if one of the following scenarios has occurred to produce mandelate terminated PLA:

i) A condensation reaction occurs between the active polymer chain end and mandelate leading to the mandelate terminated polymer.

ii) Mandelate nucleophilically attacks the PLA chain leading to cleavage of the polymer and producing a mandelate terminated polymer and free PLA, this could occur anywhere on the PLA chain.

2) The clusters of three peaks observed especially in Figures 5.3.3 a and b are the strongest indication of more than one mechanism at play in the reaction, and is difficult adequately to explain them. The first of the cluster peaks in spectrum a), 1184, 1328, 1472 etc can tentatively be attributed to the anticipated PLA + initiator (1181, [Mandelate + 14 LA +Na]$^+$, 1325, [Manedelate + 16 LA +Na]$^+$, 1469, [Mandelate + 18 LA +Na]$^+$.) The second peak in each cluster (1200, 1344, 1488 etc), cannot easily be assigned, especially as peaks from [PLA + Na]$^+$ grow in later in the reaction at 1193, 1337, 1481, 1625 etc. The third major peaks in the clusters 1218, 1352, 1496, etc can possibly be rationalised as PLA cycles containing initiator and odd numbers of LA units. (1214 [cyclic (mandelate + 15 LA)]$^+$ etc) (Figure 5.3.3e). Consistently, cycles such as these would not be expected to be observed as sodium salts.

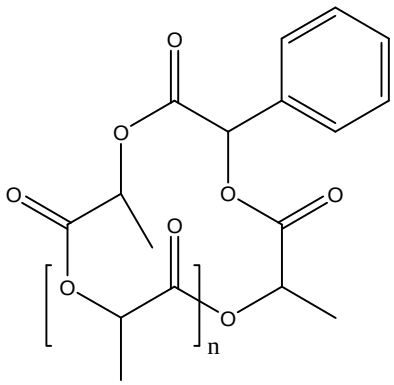


Figure 5.3.3e. Showing the structure of a PLA cycle containing one mandelate.

The formation of PLA cycles itself leads to many questions, especially as we have not observed them with any other initiator. The PLA cycles all correspond to an odd number of LA units + initiator, whereas the open chain PLA molecules initiated by sodium mandelate all have even numbers of lactate units in the chain. This suggests that cyclisation occurs not by simple elimination of NaOH or water (Figure 5.3.3f a) to give the cyclic ester, but by attack one ester unit from the end of the chain to eliminate sodium lactide or lactic acid (Figure 5.3.3f b). For the mandelate unit to remain in the cyclic polymer, this transesterification must occur by attack of the carboxylate from the terminal mandelate onto the carbon atom attached to the hydroxyl group of the terminal lactate, rather than the apparently more likely attack of the terminal alkoxide onto the chain, which would eliminate mandelate. This type of ring closing would also lead to the production of sodium lactate, which could also act as an initiator (see Section 5.2.1).

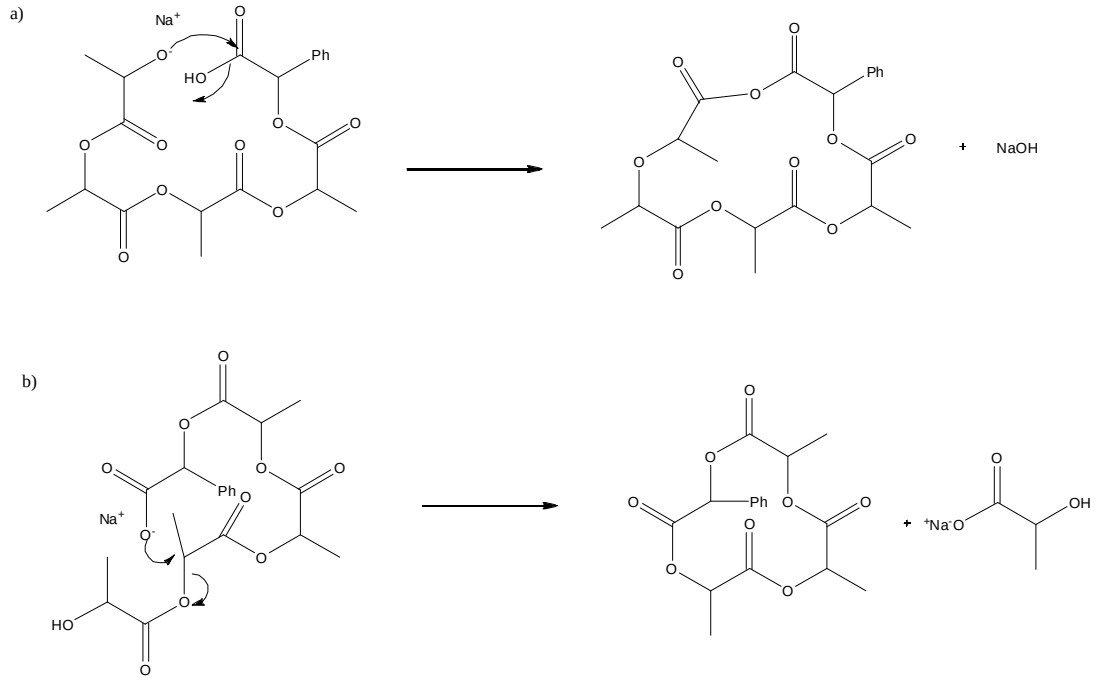


Figure 5.3.3f. a) shows cyclic ester formation. b) shows carboxylate mediated ring closing by transesterification.

3) Later in the reaction, new peaks are seen to grow. The first series (1193, 1337, 1481 etc correspond to sodium salts of PLA with even numbers of lactic acid units (1191, $[16\ LA + Na]^+$, 1335, $[18\ LA\ units + Na]^+$ etc.). Thes must arise from ring opening of lactide by NaOH. We have seen that NaOH may be released in the formation of compounds containing 2 mandelate units. The appearance of the Na[PLA] later in the reaction would be consistent with the initiation by a secondary product such as NaOH. Surpisingly PLA with odd numbers of LA units are not observed to a significant extent whether NaPLA with even numbers of lactide groups emerges, despite the fact that we have proposed that sodium lactide is a product of the formation of the proposed cyclic polymers. Polymers containing odd numbers of lactate units do appear later in the reaction, but these are almost certainly formed from inter chain transesterification reactions rather than from initiation by sodium lactate.

What can be concluded from the MALDI-TOF spectra is that, as the polymerisation proceeds the amount of free PLA increases as does the degrees of transesterification, but at a relatively slow rate compared to the transesterification witnessed with DMAP catalysed reactions. The M_n values obtained for these reactions range from 17 LA units at 60 minutes to 19 LA units at 360 minutes;

therefore there is little change, even though there is a great change in the polydistribution. The amount of unreacted lactide observed in the NMR spectrum at 60 minutes cannot be used to explain the amounts of free PLA later on, unless depolymerising to lactide is occurring concurrently, suggesting that the only mechanism that could produce free PLA in the final spectrum would have to involve elimination of mandelic acid. If the polymerisation mechanism involves the reaction proceeding through a further ring closing/ring opening mechanism, then it does explain the lack of transesterification until late in the reaction and the polydispersity observed. Previous studies on polyester ring systems show that they are an ideal method of producing polymer of narrow polydispersity and with low transesterification [7].

One of the most interesting results with mandelic acid compared to sodium PLA was that, although there was not a great difference in surface tension, the mandelic acid salts had better emulsification behaviour. This led to the speculation that perhaps increasing the bulk of the branch resulted in better emulsification behaviour. This will be discussed in depth in Chapter 6.

A test reaction carried out with mandelic acid and stannous octanoate as catalyst produced an interesting effect. In this reaction little or no polymer was formed in the reaction as the mandelic acid became bound to the tin catalyst. This complex precipitated from the melt as a white insoluble powder and NMR studies showed that free 2-ethylhexanoic acid was present in the system. An IR spectrum of the powder showed the presence of co-ordinated mandelate. The nature of the structure of the white powder is unclear, but it could be polymeric in form since there are two potential binding sites (figure 5.3.3c) (the carboxylate and the hydroxide) with bridging a possible scenario. Whatever had formed was stable and no longer reactive to lactide polymerisation. The excess of mandelate over stannous 2-methylhexanoate leads to displacement of 2-methylhexanoate and formation of stannous mandelate. The insolubility of this salt will further pull the equilibrium towards the stannous mandelate.

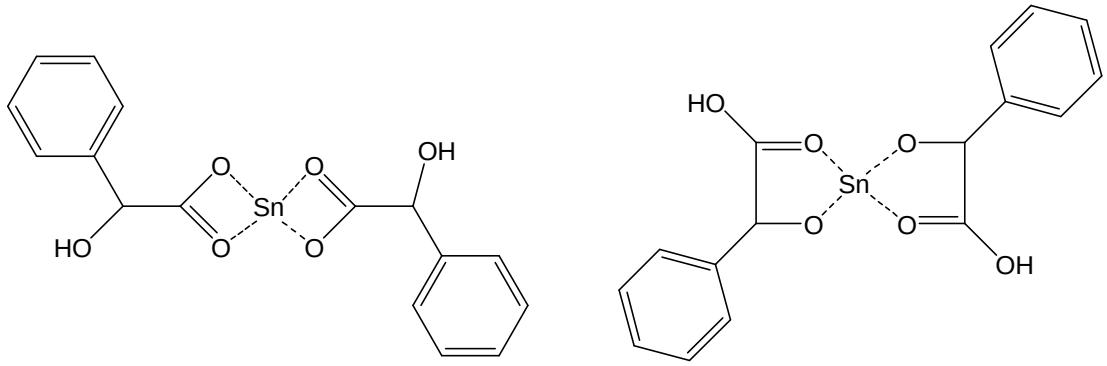


Figure 5.3.3c two of the structural isomers possible for tin mandelate.

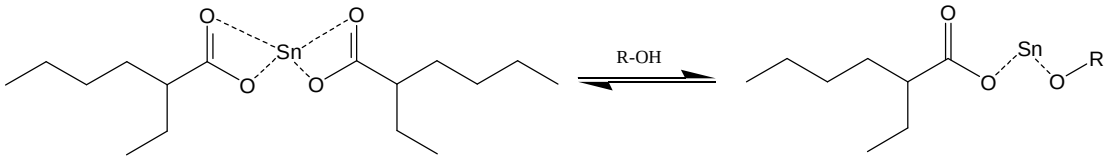


Figure 5.3.3d: A suggested structure of alkoxide species that may be formed [4].

From studies on the mechanisms of tin octanoate catalysed reactions there are trends that were noted, the first was that the presence of carboxylic acids inhibited the rate of reaction without affecting the overall polymer M_n value, whereas alcohols both speeded up the rate of the reaction and affected the overall M_n value obtained. The effect of inhibiting the reactivity is most likely associated with complete dissociation of 2-ethylhexanoate from the tin. This occurs as a result of the excess in initiator, shifting the equilibrium towards a tin mandelate salt. This resulting salt is less soluble in organic media leading to precipitation of the white solid and thus inhibiting all catalytic activity. In most $Sn(oct)_2$ mechanisms only one ethylhexanoate unit is considered to dissociate forming a tin complexed to one 2-ethylhexanoate, a lactide and an alkoxide unit, other work has suggested that during a reaction $Sn(oct)_2$ as a catalyst over time can completely dissociate all 2-ethylhexanoate to several different species including $Sn(OR)_2$, $Sn(OH)_2$ and stannous oxide [8]. The presence of the hydroxide group on mandelic acid provides the potential for bridging and hence the formation of polymeric tin complexes (Figure 5.3.3e).

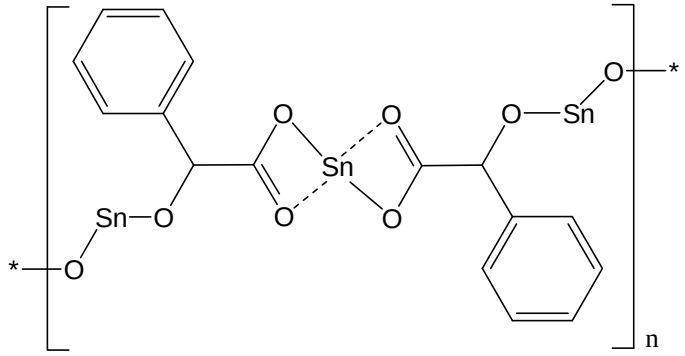


Figure 5.3.3e. Shows one possible structure of a polymeric tin complex. * oxygen could be part of carboxylate or alkoxide of mandelate.

5.4 Experimental and Results for α, β and γ-Hydroxycarboxylate Initiated PLA

5.4.1 Experimental

Materials:

Sodium Hydroxide was purchased from Fisher Chemicals.
Lactide was purchased from Aldrich and sublimed for 3 hours prior to use.
Sodium γ-hydroxybutyrate (Aldrich) was dried over P_2O_5 under vacuum prior to use.
Mandelic acid was purchased from Fisher chemicals and was converted to the sodium salt by reacting with equal equivalents of sodium hydroxide for 2 hours in water. The water was distilled off and the salt dried first in the oven then under vacuum in a desiccator over P_2O_5.
Malic acid was purchased from Fisher chemicals and the sodium salt formed using the method above.
2,2-bishydroxymethylbutyric acid (BHB) was purchased from Aldrich and converted to the sodium salt as for mandelic acid. In this case the salt could be recovered by precipitation into THF and filtered before drying.
Stannous octanoate was purchased from Aldrich and used without further purification.
Ethanol and tetrahydrofuran (THF) were used without purification.

Experimental methods for producing Sodium Salts

1) A sodium hydroxide (equimolar amount to hydroxyacid) solution was prepared in water (20 cm^3) in a clean dry plastic beaker. With stirring the hydroxyacid was added and the reaction allowed to proceed for 2 h. When finished the solution was poured into cold THF (100 cm^3) and precipitation occurred immediately. The solid was collected by filtration and dried in the oven before being transferred to a desiccator over P_2O_5.
2) The sodium hydroxide solution was prepared in a clean dry round bottomed flask equipped with stirrer bar. The hydroxyacid was then added and the solution stirred for 2 h. The water was then removed on the rotary evaporator. The solid was removed and washed with cold acetone before being dried in the oven. The product was then stored over P_2O_5 prior to use.

General experimental method for lactide polymerisation using sodium salt initiators.

To a clean dry round bottomed flask fitted with a sublimation cold finger and side arm adaptor, lactide was added and, under reduced pressure (5 mm Hg), was heated to 120 ^oC for D,L-lactide and 115 ^oC for either D or L-lactide for 3 hours. When sublimation was complete any lactide was scraped from the cold finger back into the flask and the flask was stoppered, before being completely submerged in the oil bath for 10 mins at 130 ^oC. Once molten, a stirrer bar and the sodium salt of the hydroxyacid were added in a controlled ratio. The polymerisations were allowed to proceed for the allotted time.

While still hot the polymer was poured into a cold mortar and ground to powder once cool. Samples were immediately taken for NMR spectroscopy analysis and MALDI-TOF spectrometry.

5.4.2 Results for α, β and γ-Hydroxyacid Initiated PLA

The tables below contain the experimental results obtained for polymers initiated by sodium mandelate, sodium 2,2-bishydroxymethylbutyrate and sodium GHB.

5.4.2a Sodium Mandelate Initiated PLA Polymers.

Table 5.4.2a. Results of reaction initiated by sodium mandelate.

Ratio L : I	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6[a] : 1[b]	25 mins	13	144 *	5	49.65
12[a] : 1[b]	60 mins	17	144 *	5	50.225
6 : 1	40 mins	16	144	5	44.5
12 : 1	50 mins	17	144	4	_
20[c] : 1	60 mins	~ 40	72 - NaPLA	3	_
12[a] : 1	80 mins	22	144	4	_
* 12 : 1	60 mins	25	144 - NaPLA	4	_
* 12[a] : 1[b]	60 mins	22	144	4	_

[a] L-lactide was used; [b] Sodium L-Mandelate was used; [c] D-Lactide was used; * clusters of peaks with 144 separation

5.4.2b NaBHB Initiated PLA Polymers.

A series of test reactions was carried out using a 12 : 1 (L : I) ratio.

1) A test reaction was carried out using Sn-oct as a catalyst. The reaction was carried out at 130 ^{o}C for 30 mins. The polymer produced had ~10 LA units per arm. It was suggested by the MALDI-TOF that the products were predominantly diblocks (containing 2 BHB units) and triblocks (3 BHB units) in this instance. It can be suggested that the BHB units are joined through PLA chains, and that this may have occurred as a result of chain transfer, since the odd numbers of LA units are present in some cases. The peak at 1256 amu can be as attributed to 2 BHB units and 13 LA units (936 amu). The peak at

1467 amu can as attributed to 3 BHB units and 12 LA units (864 amu). The M_w of the triblock continues to increase up to ~ 34 LA units (2448 amu).

2) A second reaction was carried out where NaOH was used as a catalyst. The reaction was carried out at 130 ^oC for 30 mins. The polymer produced was predominantly the BHB initiated polymer ~ 10 LA units per arm. This polymer had a surface tension of 47.8 mN/m at 1mg cm^{-3} concentration.
3) A third reaction was carried out this time employing Na lactate as the catalyst. This was an attempt to ascertain whether the cation could preferentially transfer to one of the sites on the BHB molecule. In this case the polymer showed an M_n of 10 LA units. The MALDI-TOF spectrum shows mostly BHB initiated polymer ranging from ~ 10 LA (5 per arm) units to 32 LA units (16 per arm), separation shows that little to no transesterification has occurred (144 separation). There is little indication that sodium lactate has produced any NaPLA.

Results of NaBHB reactions are shown in the table below.

Table 4.5.2b. Results for reactions carried out using sodium 2,2-bishydroxymethylbutyrate.

Ratio (L : I)	**Reaction Time**	**M_n (LA's per arm)**	**MALDI-TOF Distribution (amu)**	**Surfactant Quotient**	**Surface Tension (mN/m)**
12 : 1	40 mins	14	144	5	_
6^a : 1	60 mins	6	144	5	45.53
12 : 1	15 mins	14	144	5	_
12 : 1	30 mins	8	144	5	47.75
6 : 1	40 mins	6	144	5	_
* 12 : 1	60 mins	6	144	5	_
* 12^a : 1	60 mins	11	144	5	_

[a] L-lactide was used

5.4.2c NaGHB Initiated PLA Polymers.

Table 5.4.2c Results for reactions carried out using sodium GHB as initiator.

Ratio	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6[a] : 1	40 mins	14	72	5	_
6 : 1	40 mins	14	72 free PLA	5	_
12[a] : 1	10 mins	28	72	5	_
6 : 1	30 mins	_	72	5	46.2

[a] L-lactide was used;

5.5 Synthesising Other α-Hydroxyacid Salts for Lactide Polymerisation

As well as the naturally occurring salts it seemed prudent to investigate other α-hydroxyacid salts for lactide polymerisation in order to establish the effect of steric bulk adjacent to the hydroxyl group. The aim was to prepare initiators with branches of 2-6 carbon atoms in length. As many of these initiators are either not natural compounds or are not commercially available they had to be synthesised from their respective α-halides or amides.

Figure 5.5 shows the structures of the initiators that were prepared and tested in lactide polymerisation and the subsequent physical properties of the polymers.

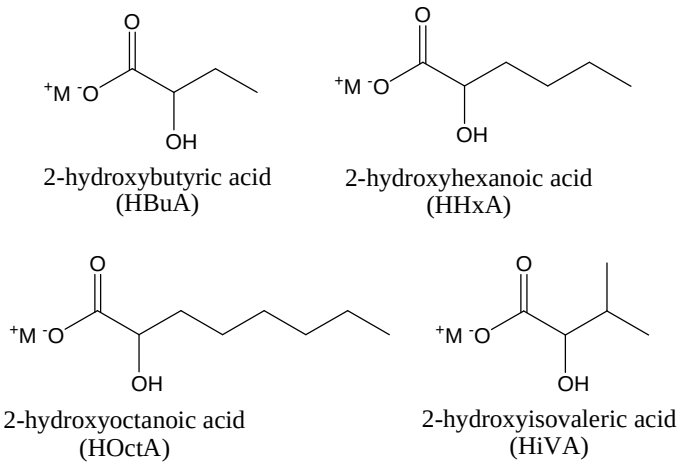


Figure 5.5 showing the structures of the other alkali metal α-hydroxycarboxylates used in lactide polymerisation.

The differences in adjacent chain length or bulk should produce interesting properties in terms of surfactant and emulsification behaviour, as it provides a deviation from the ideal model of a surfactant. It should also have an effect by limiting the packing efficiency of PLA molecules in the solid and solution phase.

5.5.1 2-Hydroxybutyrate Salts for Lactide Polymerisation (Ethyl)

2-hydroxybutyrate initiator was prepared from the corresponding chloride (by oxidation in water, in the presence of potassium carbonate) and was used to increase the steric bulk of the adjacent group to C_2H_5. The solubility in molten lactide was still very good. The polymers produced have predictable M_n values and show good surfactant and emulsification properties.

The acidity of this group can be considered as similar to that of lactic acid itself, there is a little free PLA produced in these reactions.

Results:

Table 5.5.1. Results for PLA initiated using sodium 2-hydroxybutyrate

Ratio	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6[a] : 1	40 mins	16	_	4	47.33
12[a] : 1	60 mins	25	144 amu	3	49.5
12 : 1	40 mins	21	144 amu	4	45.68

[a] L-lactide was used

5.5.2 2-Hydroxyhexanoic Acid for Lactide Polymerisation (Butyl)

During the initial test reaction using this initiator where Sn-oct was supposed to be used as catalyst, the 2-hydroxyhexanoic acid polymerised the lactide before the catalyst was added. This was somewhat unexpected. However there were only two reasons for this to occur. The first was that it had carried out ROP by an acid mediated process; the second that, during the production of 2HHxA, some of the

potassium salt was formed. After 10 mins in this reaction a polymer of M_n 12 LA units was formed with approx 86% conversion of lactide, this changed on addition of tin catalyst to M_n 16 LA units and approx 95% conversion.

To test the effect of acid, a reaction was carried out using 2-ethylhexanoic acid and octanol as the initiator. Even after 2 hours, little to no PLA was formed. However, the MALDI-TOF confirmed that the polymer did contain some potassium ions, suggesting that adventitious salt was the initiator. The potassium hydroxyacid salts, are somewhat better at polymerisation than the sodium salts in terms of conversion of lactide and reaction times. There is little difference however seen in the surfactant or emulsification properties.

Results:

Table 5.5.2. Results of reactions initiated using sodium 2-hydroxyhexanoate

Ratio	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6 : 1[a]	40 mins	16	144	4	_
6[b] : 1	40 mins	7	144	5	46.68
12[b] : 1	60 mins	24	144	5	47.5
6 : 1	40 mins	10	144	5	40.08
12 : 1	60 mins	16	144	5	44.48
*12 : 1[a]	60 mins	22-23	144	5	_
*12[b] : 1[a]	60 mins	26-27	144	5	_

[a] KHHxa was used as initiator; [b] L-lactide was used; * Indicates Bulk sample.

5.5.3 2-Hydroxyoctanoic Acid for Lactide Polymerisation (Hexyl)

On increasing the chain lengths of the initiator group there are two aspects that become immediately apparent. The first is that the initiator becomes more soluble in the molten lactide, and the second is that longer reaction times are generally required. The water solubility of the polymers produced using this initiator is greatly reduced although there is some benefit to the emulsification behaviour.

Results:

Table 5.5.3. Reactions initiated using sodium 2-hydroxyoctanoate

Ratio (L : I)	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6 : 1	80 mins	15	144 + 72	5	agg
12 : 1	60 mins	26	72	3	agg
12[a] : 1	45 mins	26	144	2	agg
6[a] : 1	45 mins	16	_	5	agg
*12 : 1	60 mins	24	_	4	agg
*12[a] : 1	60 mins	24	_	4.5	agg

[a] L-lactide was used; * Polymers were produced in bulk; agg – surface tension could not be measured due to fast rate of aggregation.

5.5.4 2-Hydroxyisovalerate Salts for Lactide Polymerisation (Isopropyl)

This initiator was the most interesting of all the α-hydroxyacids as it was the only one where different enantiomers of the initiator could be used to ascertain whether this had any effect on the polymerisation. The simplest to prepare is 2-hydroxyisovaleric acid as it can be produced from the essential amino acid valine, which can be purchased either as the racemate or in the D or L form. The oxidation of valine (in water) to hydroxyisovaleric acid is an S_N2 reaction, which leads to inversion of the stereochemistry, therefore for L-hydroxyisovaleric acid, it is necessary to start with D-valine etc.

In terms of reaction rates etc there was little difference in the reactions between the enantiomerically pure initiator and the racemate. Results with the enantiomerically pure version with different enantiomers of lactide yielded only differences in the physical characteristics, as the L-HiVA produced more crystalline polymers with L-PLA etc. When L-HiVA was used with L-lactide, the polymer produced actually showed slightly better surfactant and emulsification properties, although in this case it was also noted that there were more free PLA chains.

As well as carrying out a reaction with the NaHiVA, two reactions were carried out with valine. One reaction used stannous octanoate, as amines are nucleophilic enough to ring open lactide. This reaction was carried out to see the effect of unreacted valine in the system and to ascertain whether it was likely to be significant in lactide polymerisation. The effect was that valine does react very well with lactide in the presence of catalyst. Sodium valinate was also shown to be a very potent initiator for lactide polymerisation.

Results:

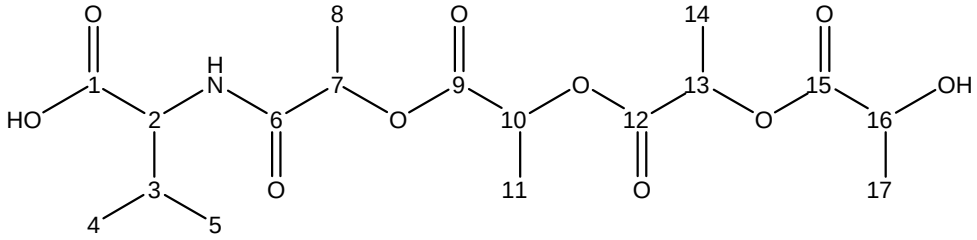
Table 5.5.4. Reactions initiated using sodium 2-hydroxyisovalerate.

Ratio	Reaction Time	M_n (LA's)	MALDI-TOF Distribution (amu)	Surfactant Quotient	Surface Tension (mN/m)
6[a] : 1	25 mins	17	144	5	46.175
6[a] : 1[b]	25 mins	9	72	5	_
12[a] : 1	40 mins	13	72[c]	5	46.85
6 : 1	30 mins		72	5	
6 : 1	30 mins	14	144[d]	5	46.1
12 : 1	60 mins	27-29	144	5	47.2
12 : 1	60 mins	26	144	4.5	_
12[a] : 1	60 mins	24-25	144	5	_

[a] L-lactide was used; [b] NaHiVA was prepared from 2-bromoisovaleric acid; [c] Polymer possibly dimer a lot of free NaPLA also present; [d] dimodal distribution indicating free NaPLA from transesterification.

Reactions with valine:

1) Using Sn-oct as catalyst and at 10 :1 (L : I) ratio for 30 mins at 130 ^{o}C. produced a polymer with M_n approximately equivalent to 8-9 LA units. No transesterification was observed however the catalyst largely decomposed as shown from the ^{13}C NMR spectrum. From the MALDI-TOF there was no indication of any free PLA peaks, however there were two polydistributions 16 amu units apart. This could indicate some cyclisation occurring. Importantly the separation was 144 amu indicating little to no transesterification. Possibly as a result of dimerisation etc. the polymer was insoluble in water.



^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 11.75(CH_3, 2-ethylhexanoate), 15.79(CH_3, lactide), 16.67, 16.73, 17.64, 17.82 & 17.88(CH_3, C-8,11,14), 18.91(CH_3, 2-ethylhexanoate), 20.48(CH_3, C-17), 22.61, 25.18, 29.50 & 30.99(CH_2, 2-ethylhexanoate), 31.47 (CH_3, C-4,5), 46.95(CH, 2-ethylhexanoate), 56.85(**C**NH-PLA), 66.67 & 66.71(**C**H(CH_3)OH, C-16), 69.01, 69.20, 69.28 & 69.51(**C**H(CH_3)O, C-10,13), 71.58 & 71.70(**C**H(CH_3)O, C-7) 72.48(lactide), 167.46(lactide), 169.18, 169.38 and 169.63(C=O, C-6,9,12,15).

2) Using Sodium Valinate 9 : 1 (L : I) ratio at 130 ^{o}C for 30 mins.

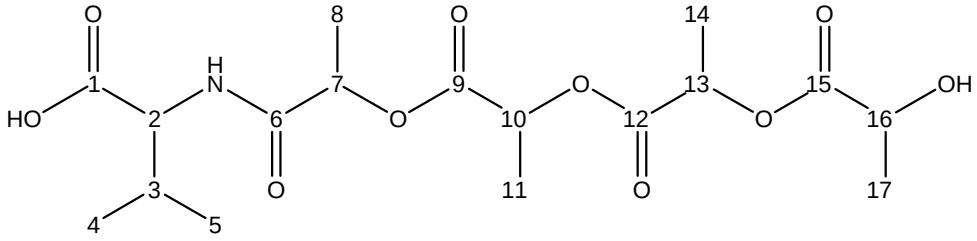
Sodium valinate was prepared by dissolving sodium hydroxide (1 equivalent) in methanol, adding valine (1 equivalent) and stirring at RT for 2 hours. The methanol was removed on a rotary evaporator and the product dried for a further hour in an oven at 80 ^{o}C. The ^{13}C NMR spectrum does not show conclusively that the valine was incorporated, due to the strong PLA peaks. What is interesting to note here is that the racemate D,L-lactide was used, but the ^{13}C splitting is more consistent with enantiomerically pure lactide. As the racemic D,L-valine was also used this might be indicative of some preference with the initiator that is not encountered with the hydroxy species, which could lead to stereocomplexes forming, i.e two enantiomerically pure stereo-opposite polymer chains.

However from the MALDI-TOF mass spectrum there are no peaks corresponding to free PLA, although the separations are 144 amu. The MALDI-TOF spectrum seems to agree with a system containing valine but being the di-cationic salt (2 Na^+ ions). There are two theories as to why a di-sodium species would be present:

1) there has been fragmentation of a longer polymer chain into two, therefore we are seeing only half the true Mwt.

2) The sodium salt remains located at the alkoxide, the disodium species is formed due to the sodium of the MALDI-TOF matrix interacting with the acidic carboxylic acid.

In this case there is only one prevalent polymer distribution. This polymer had a surfactant quotient of 5 and a foam stability greater than the NaHiVA counterpart.



^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 15.83(lactide), 16.66 & 17.79(CH_3, C-8,11,14), 19.47 & 20.07(CH_3, ?), 20.51(CH_3, C-17), ~31(CH_3, C-4,5), 66.61(**C**(CH_3)OH, C-16), 69.02 & 69.20(**C**H(CH_3)O, C-10,13), 71.80(**C**H(CH_3)O, C-7), 169.39 and 169.63(C=O, C-9,12,15).

5.5.5 Conclusion

PLA sodium salts are easy to produce, green alternative surfactants. In Chapter 6 the physical characteristics and rheology of these polymers will be discussed in greater detail. From a synthetic point of view these polymers successfully fulfil the research criteria. They can be produced with no toxic catalysts as sodium and potassium are essential elements to the body – the field could possibly be extended with a look at the alkaline earth metals, such as calcium and magnesium as they are already well established ROP initiators for living polymerisations.

The alternative sodium salt initiators such as NaBHB, NaMan and NaHiVA continue the trend of green initiators as they are all produced from naturally occurring chemicals. Above all others they also offer the most interesting research futures, as they have all shown the ability to form diblocks, and under the right circumstances could produce continuous random chains where HiVA or mandelate units offer a deviation from the PLA chain. BHB has already been used to produce copolymers

with branched or hyperbranched structure. However, there are many possibilities to pursue with regard to the uses of these molecules. It may be possible using the sodium salts to tailor the shape of these molecules as they polymerise depending on the choice of solvent. If the molecules re-organise themselves to maximise/minimise hydrophobicity/hydrophilicity then it may be possible to alter the shape of these molecules as polymerisation occurs.

As further work it may be beneficial to look further at amino acids as initiators for lactide polymerisation. There is a much wider scope available here as the numbers of α-aminoacids and shape variations are fairly extensive. There are also possibilities of extending to more branched systems, or producing more polar head groups. These would be interesting to look at in terms of colloidal systems for biomedical applications or for personal care applications as the essential amino acids would have few side-effects. Figure 5.4.5 shows a list of possible amino acids that are readily available.

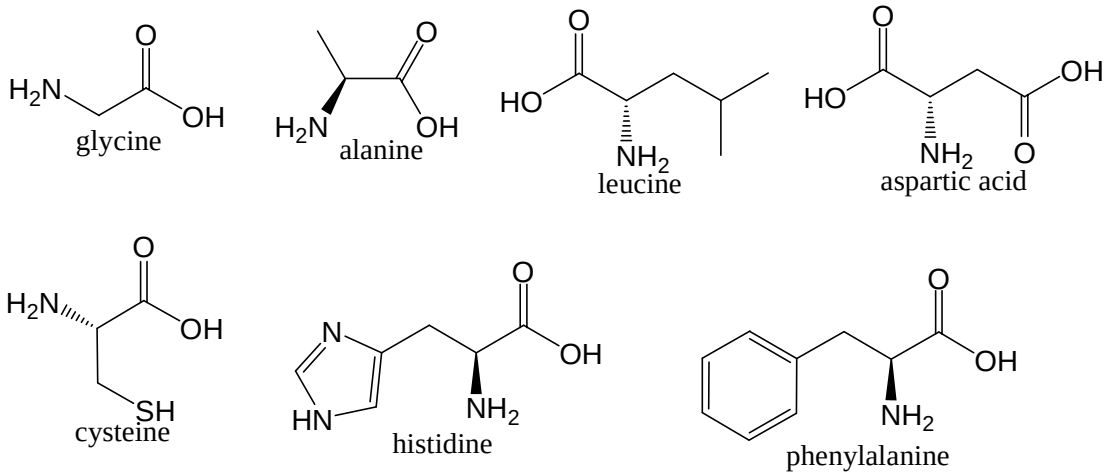


Figure 5.5.5 shows a list of commonly available aminoacids for further development into PLA surfactants.

5.6 PLA Sodium Salt Stereoblocks.

There are many copolymers of PLA that have been produced with a great deal of focus on solvation properties (hydrogels) and physical characteristics such as flexibility, strength and optical properties. The most common of these copolymers are PEG copolymers [9], poly(ε-caprolactone) [10], and poly(glycolic acid) [11, 12] copolymers. There is, however, another category of PLA copolymers that has been produced and these are known as PLA stereoblocks. In these copolymers there are, as well as repeat units of LA, repeat units of stereochemical blocks of defined tacticity. These blocks can consist of Isotactic PLA or syndiotactic PLA and be many combinations of each.

In 2000 Coates *et al*. [13] produced a stereoblock polymer in a one pot procedure using a chiral aluminium alkoxide catalyst. In work prior to this, reaction with a chiral catalyst and D,L-lactide resulted in either isotactic polymers produced preferentially from a single enantiomer [14] or two enantiomerically pure chains [15] forming the stereocomplex (blend). Coates [13] reports that the stereoblocks, as analysed by the ^{1}H NMR spectroscopy, contained approximately 11 lactide (22 LA) units per block.

In the simplest case if we look at L and D-lactide they both produce isotactic PLA. However there is a phase difference between these two chains. Thus, combining them together forms a stereoblock of a sort, as the regularity is slightly altered. This can only be regarded as a true effect if the chain is capped at the end by a non-LA group or by the presence of a sodium cation etc. As the true difference between L and D lactide is much like the difference between sin and cosine (repeat unit lies out of phase). A more significant change is observed if meso-lactide or D,L-lactide is used. Figure 5.6 illustrates these differences by showing various tetrad sequences and how they combine to form a di-stereoblock.

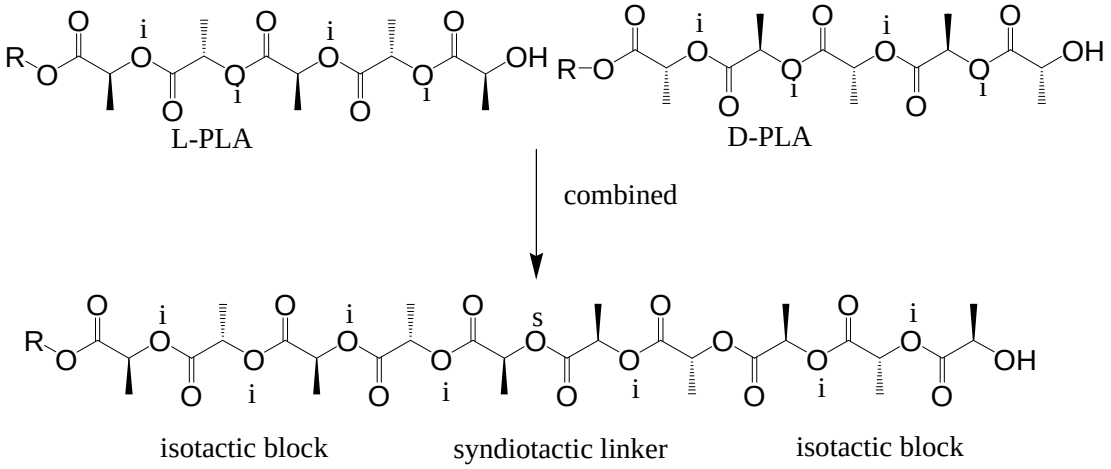


Figure 5.6. Shows the formation of a di-stereoblock.

By addition of more initiator after an initial polymerisation period it is possible to combine different blocks of isotactic or heterotactic units, more complicated systems of A-B or A-B-A containing variations on the stereochemistry of the chains.

5.6.1 Stereoblocks Formed by Sodium Lactate Initiation.

Since sodium lactate does not possess the chiral ligands of the aluminium system, so a one-pot process leading to stereoblocks is unlikely. The only method open here regarding stereoblock formation is a 2-step system whereby the polymerisation of L, D or D,L-lactide is carried out before adding a quantity of a different monomer. Through prior experiments it was established that an M_n of approximately 20-24 LA units is ideal for emulsification purposes and has reasonable surfactant properties also. Therefore the overall monomer to initiator ratios was adjusted to a maximum of 16:1. The formation of stereoblocks used the same polymerisation procedures as before, only a second batch of lactide was added after an allotted time and the polymerisation allowed to proceed until complete.

The types of stereoblocks produced are described as *Soft* (D,L) or *Hard* (L and D) and a list of these polymers was produced to analyse:

NaO---- Hard----Soft

NaO----Soft----Hard

NaO----Soft----Hard----Soft

NaO----Hard----Soft----Hard

NaO----Soft----Hard(L)----Hard(D)

These polymer structures were also produced for polymer blending which will be discussed in the next section. There were no clear advantages of using stereoblocks over normal polymers for surfactant applications or emulsions. These polymers seem to aggregate faster than singular chains, which made carrying out surface tension experiments next to impossible, suggesting that this alteration of the degrees of order lowered the CMC, resulting in rapid aggregation. This holds true in most cases.

5.6.2 A-B Type Stereoblock PLA

There were several A-B type stereoblocks produced; a soft-hard, hard-soft and hard-soft of different chain block length. It can be seen from the NMR results that the conversion of lactide is not complete in all these cases, but the amounts unreacted are not overly problematic. It can also be noted from the NMR that the chains retain their stereo-purity, as seen by the 2 peaks around 69 ppm, indicating the absence of further tetrad sequences. Even where D,L-lactide is used as a block the NMR shows this higher degree of order that would not be present in a normal D,L-lactide polymerisation.

In terms of surfactant ability having the soft segment at the end produced better solubility and foaming. When the hard segment was at the end coagulation and sedimentation occurred faster. What is clear from the results is that this methodology can be successfully employed using Na lactate etc to produce well-defined polymers with predictable molecular weights, which agrees with the mechanism for a living polymerisation.

General stereoblock polymerisation procedure:

To a clean dry round-bottomed flask, lactide was added and heated to 130 ^{o}C, in an oil-bath until molten. The initiator was then added in a controlled ratio and the

polymerisation allowed to proceed for a given time. A sample of the polymer was then taken for NMR analysis, before a further quantity of a different lactide monomer was added and reaction proceeded for the allotted time. All monomer was sublimed at 115 ^{o}C for 2-3 hours prior to use. The above step was repeated if a tri-stereoblock was required. Once the polymer was produced samples were taken for NMR and MALDI-TOF and the polymer was transferred in the molten state to a mortar before setting and grinding.

Results:

Table 5.6.2. Results obtained for A-B type stereoblock PLA.

Ratio (L : L* : I)	Reaction Time	M_n 1st Segment (LA u nits)	M_n 2nd Segment (LA units)	Mass Distribution	Surfactant Quotient
$6^a : 6^b : 1$	35 mins + 35 mins	12	24	72 + 144 amu 10 to 41 LA units	4
$6^b : 6^a : 1$	35 mins + 35 mins	12	27	72 amu 10 to 35 LA units	5
$6^b : 4^a : 1$	45 mins + 20 mins	12	21	_	4.25
$6^c : 6^a : 1$	30 mins 30 mins	12	24-25	144 amu 11 to 41 LA units	5
$6 : 6 : 1^d$	30 mins 30 mins	13	26	144 8 to 40 LA units some free NaPLA	4

L* denotes different monomer used; [a] D,L-lactide soft segment; [b] L-lactide hard segment; [c] indicates that D lactide was hard segment; [d] indicates NaHiVA was used as initiator.

5.6.3 A-B-A Type Stereoblock PLA

Using the same methodology described before tri-stereoblocks of PLA can be produced. The overall M_n was again limited to 24-30 LA units for the sake of solubility etc. Only two of these polymers were produced for comparative purposes the Hard-Soft-Hard and Soft-Hard-Soft. The NMR spectrum is less useful in this instance as the stereoblocks are shorter so that the tetrad sequences are much less defined. There are three peaks in each suggesting a D,L-lactide type structure with

low transesterification. The MALDI-TOF confirms that little transesterification has occurred.

In terms of the surfactant and emulsification behaviour of these two samples, the Hard-Soft-Hard polymer produced had better emulsification behaviour and retained good water solubility and foaming. The Soft-Hard-Soft polymer showed little to no emulsification behaviour but retained good surfactant properties.

Results:

Na-L-D,L-L-PLA (Hard-Soft-Hard):

Polymer was prepared using a ratio a ratio of 4 (L) : 4 (D,L) : 4 (L) : 1.
M_n from 1st step: 9 LA units
M_n from 2nd step: 14 LA units
M_n from 3rd step: 24 LA units.

^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 15.82(CH_3, lactide), 16.66, 17.08 & 17.62(CH_3, PLA), 20.51(CH_3), end group), 69.02, 69.20 and 69.65($CH(CH_3)O$, PLA), 72.48(lactide), 169.38 and 169.63(C=O).

The mass distribution (as seen in figure 5.6.3a) from MALDI-TOF mass spectrometry shows some but little transesterification, 144 separation predominantly except at higher molecular weights, and mass ranges from 10 LA units (761 amu) to 35 LA units (2561 amu).

Surfactant quotient: 5 as it showed good solubility and foaming.

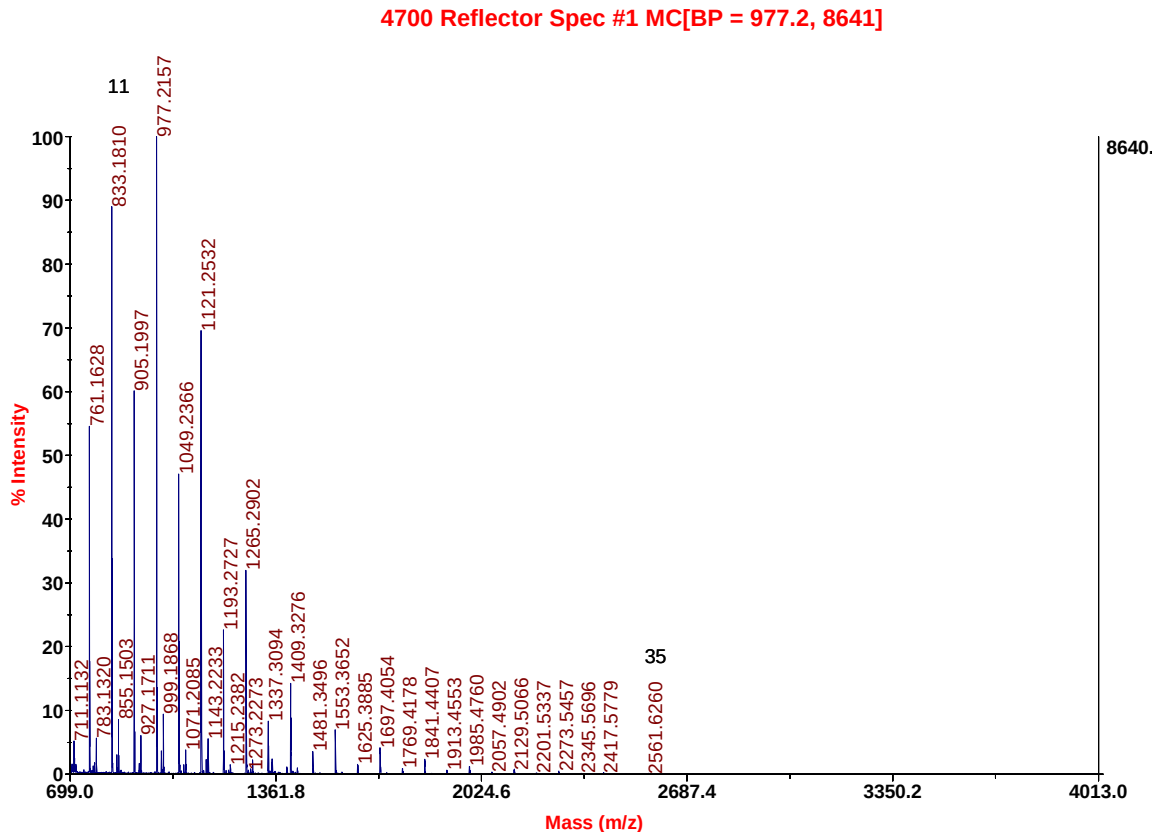


Figure 5.6.3a. MALDI-TOF spectrum of the Hard-Soft-Hard stereoblocks copolymer.

Na-D,L-D-D,L-PLA (Soft-Hard-Soft):

Polymer was prepared using a ratio a ratio of 4 (D,L) : 4 (D) : 4 (D,L) : 1.
Overall M_n after third step: 25-26 LA units.

^{13}CNMR ($CDCl_3$, 75 MHz) δ(ppm): 15.83(CH_3, lactide), 16.66, 17.15 & 17.63(CH_3, PLA), 20.51(CH_3), end group), 66.63($CH(CH_3)OH$, End group) 69.03, 69.20 and 69.45($CH(CH_3)O$, PLA), 72.48(lactide), 169.38 and 169.62(C=O).

The mass distribution (as seen in figure 5.6.3b) from MALDI-TOF shows some transesterification although 144 amu separation is again predominant. The mass ranges from 10 LA units (761 amu) to 34 LA units (2849 amu).

Surfactant Quotient: 3, polymer had poorer water solubility and low amount of foaming.

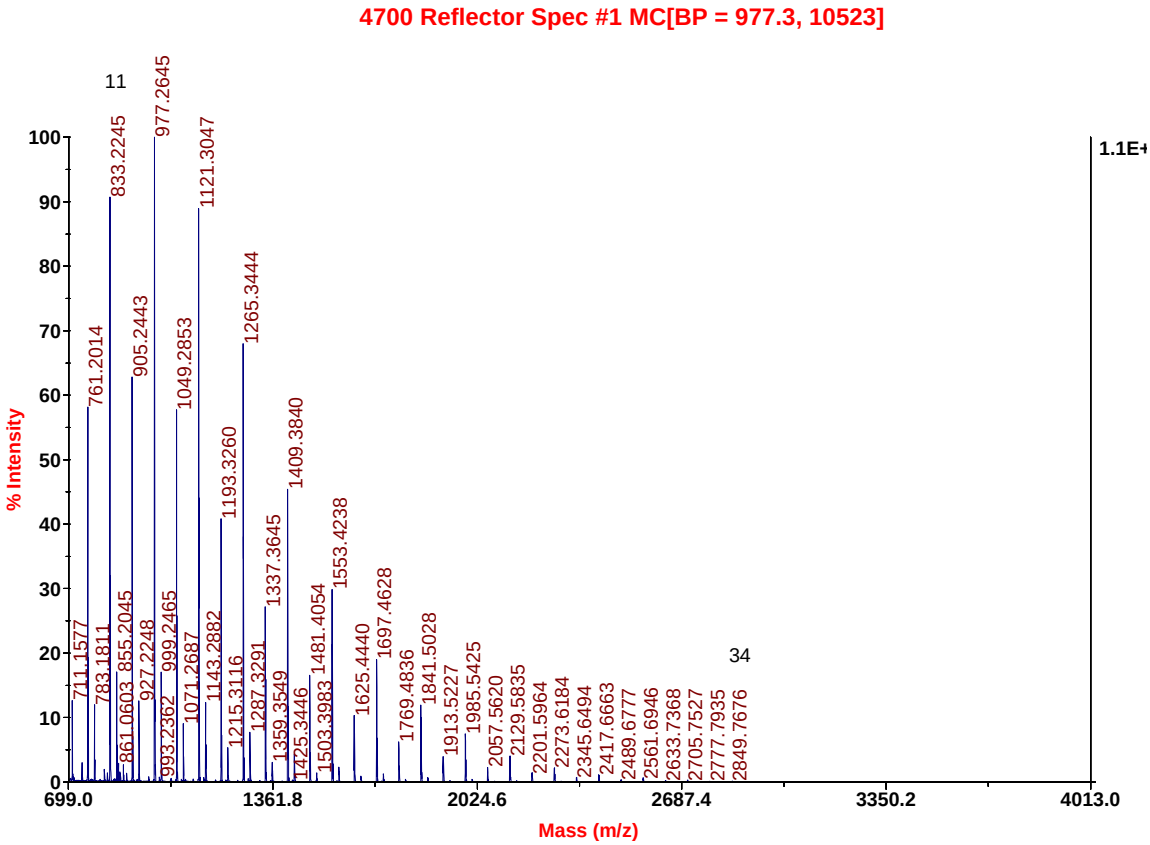


Figure 5.6.3b. MALDI-TOF spectrum of the Soft-Hard-Soft stereoblocks copolymer.

5.6.4 Conclusion

The PLA stereoblocks are worth more investigation into their use as surfactants, as they offer a possibility for tailoring the polymers to a specific use. This could be achieved by using different initiators or simply by further altering of the monomer ratios. For future work it could also be used in conjunction with ROP of ε-caprolactone etc, to add soft segments to the polymer structure. From the results presented it is clear that the ordering of the segments does play some significant role in the simple surfactant properties, a more in depth discussion on the structural differences can be found in chapter 6

5.7 PLA Sodium Salt Blends.

Using the same principle that metals may be blended to form alloys, resulting in different physical properties, so too can polymers be blended. Common polymers produced using this methodology are rubber for car tyres, as the polymers produced can have enhanced mechanical strength, increased elasticity etc.

There are many methods available for producing polyblends [16]:

1) Mechanical blends are when the polymers are mixed at temperatures exceeding the T_g (glass transition temperature) or T_m (melting point)
2) Solution cast blends are when polymers are dissolved in a common solvent (usually at saturation point) and mixed. The solvent is then removed resulting in a blend
3) Latex blends occur when the polymers are finely dispersed in water and mixed leading to coagulation.
4) There are also chemical blend processes where monomers may be mixed together and homo-polymerised. The resulting polymeric blend usually contains lots of cross-linked networks.

Stereocomplexes are polymeric blends of enantiomerically pure polymer with its stereo counterpart. In this case from blending D and L-poly(lactic acid). Work by Ikada *et al*. has focussed on different approaches to stereocomplex formation by direct melt blending [17] and by use of concentrated solutions [18]. They discovered that if D-PLA and L-PLA are mixed together in solution in an equal ratio (and the polydispersities have to be almost identical) they will undergo a physical change from a highly crystalline solid to an amorphous gel. This also resulted in sol-gel behaviour in the concentrated polymer solution.

The reason for this physical change has been put down to thermally irreversible cross-linking or crystallites, resulting in stronger interactions. How strong these interactions are between PLLA and PDLA may stem from the helical nature of PLA in relation to how it packs. Whether it is the α or β helix that is responsible for the gelation behaviour is unknown as both are known to exist in solution spun PLA

[4]. Due to the stereochemistry an α-helix of PLLA rotates differently to the α-helix of PDLA, this may result in a difference in degree of interaction than is seen in pure PLA.

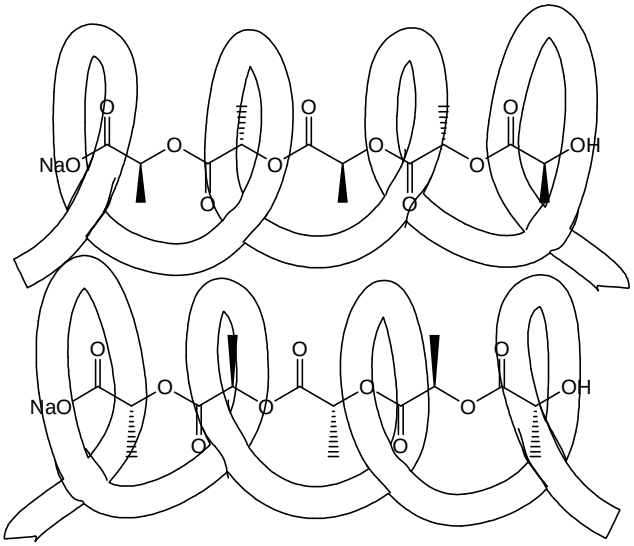


Figure 5.7. Shows the α-helical structures of PLLA and PDLA and how they might conceivably combine.

It might not be completely clear but two or more PLLA molecules should be able to stack directly on top of each other maximising the electrostatic interactions – resulting in higher crystallinity, however when combined with the PDLA (which turns in the opposite direction) they are unable to stack in the same way. If the electrostatic interactions are weaker this results in less crystalline behaviour like that known with D,L-PLA. It could be hypothesised that the stereocomplex (blend) interacts better out of phase resulting in the two chains being able to freely move across each other and this added mobility would lead to cross linking and threading of the polymer chains.

5.7.1 Concentrated Solution Blends of L-PLA and D-PLA.

The concentrated solutions method was chosen as the best method of blending in the case of NaPLA salts so as to minimise transesterification and chain transfer due to the living chain ends of each polymer. Dichloromethane was chosen as the ideal solvent as it has a low boiling point and is a medium in which the polymers are highly soluble. Different approaches were examined for removal of the polymer including precipitation of the concentrated solution into diethyl ether, but this was only possible at ratios greater than 12 : 1. With short length of polymer chains this method was

unsuccessful, as precipitation was rapidly followed by resolvation. In order to produce the desired mixtures the solvent was either removed on the rotary evaporator or allowed to evaporate slowly into the atmosphere.

Choosing the right method seems to be quite important in terms of gel formation. In the only case where a gel was formed, the polymer was treated as described by Tsuji and co-workers [18]. Here the concentrated solutions were mixed and stirred for 1 hour before precipitating into diethyl ether. In this case no precipitation occurred, and the solvent was removed on the rotary evaporator, leaving the stereocomplex gel. The polymer was then placed under vacuum on a Schlenk line for two hours to remove the final traces of solvent. Interestingly the gel that formed was less water-soluble than any of the powders even with sonication. This is probably a by-product of how randomly the PLA molecules are oriented in the material. The level of interaction is such that the gel packs together both to obstruct the penetration of water and to obscure the cations (hydrophilic portion) of the molecule reducing any polar interactions. Conceivably if the same polymer were mixed in a more polar solvent it would maximise the available sites of water interaction.

As a placebo type reaction two Na D,L-PLA polymers of equal ratio were blended, in this case there should be no change in any of the overall characteristics. The only change was a shift in the M_n value by ~ 1 LA unit which is not greatly significant given any error in measurement. The only other factor in this reaction was that the MALDI-TOF spectrum showed a preference of even over odd, suggesting some transesterification or inter-chain reactions had occurred.

General Procedure:

Reactions of D and L-lactide were carried out simultaneously using the previously described methods, where sodium lactate, sodium hydroxyisovalerate or sodium mandelate were used as initiators. Once the polymers had formed samples were taken for NMR analysis and the polymers once cooled were dissolved in dichloromethane. Once the polymer had completely dissolved the volume of solvent was reduced to 15-20 mls before the two polymers were mixed. The mixed polymers were then:

1) Stirred for 1 hour before the solvent was completely removed on the rotary evaporator.
2) Stirred for 1 hour and then precipitated into 50-75 mls of diethyl ether, filtered and dried.
3) Stirred overnight at room temperature allowing the solvent to slowly evaporate into the atmosphere. This was followed by drying *in vacuo* at 35 ^{o}C on a Schlenk line.

Results:

Table 5.7.1. Results of stereoblends of L and D-PLA

Ratio (L : I)	Reaction Time	Blend Type	M_n L-PLA (LA u nits)	M_n D-PLA (LA units)	Overall M_n (LA units)	Mass Distribution	Surfactant Quotient
9 : 1[a]	30 mins	1	17	17	19	144 amu 8 – 34 LA's	_
9 : 1[b]	40 mins	2	18	16	17	144 + 72 amu 7-37 LA's	5
9 : 1[c]	45 mins	2	15	15	17	144 + 72 amu	_
12 : 1[b]	80 mins	2	28	28	27	144 + 72 amu 10 – 37 LA's	5
10 : 1[b]	60 mins	3	19	19	19-20	144 + 72 amu 10 – 38 LA's	_
8[d] : 1[b]	40 mins	1	18	18	19	144 + 72 amu 10 - 31 LA's	5

[a] NaHiVA was used as initiator; [b] sodium lactate was used as initiator; [c] sodium mandelate was used as initiator; [d] two D,L-lactide polymers were blended.

5.6.2 Blending Opposing Stereoblocks.

Combining the methods both developed from preparing stereoblocks and blends, it was also worth seeing if the stereoblocks underwent similar types of interactions in the blend. To illustrate this, three blends were prepared consisting of:

Na-Hard(L)-Hard(D) + Na-Hard(D)-Hard(L)

Na-Soft-Hard(D) + NaSoft-Hard(L).

Both of these blends were prepared using blend type 2 and neither showed any gelling behaviour. The surfactant behaviour of these polymers was similar to that already seen by the stereoblocks and aggregation occurred quickly.

Results:

Table 5.7.2. Results of blending stereoblocks of PLA.

Ratio (L : L : I)	Reaction Time	Blend Type	Overall M_n (LA units)	Mass Distribution	Surfactant Quotient
6^a : 6^b : 1 + 6^b : 6^a : 1	30 mins + 30 mins	2	–	72 amu 10 – 45 LA's	–
5^c : 5^a : 1 + 5^c : 5^a : 1	30 mins + 30 mins	2	24	72 amu 8 – 44 LA's	5

[a] L-lactide monomer; [b] D-lactide monomer; [c] D,L-lactide was used as monomer.

5.6.3 Conclusion

Blending stereoblocks or blending to form stereocomplexes may offer a higher degree of flexibility in the uses of NaPLA salts in terms of personal care applications where powders are not sufficient. A great deal more research needs to be carried out into the properties of these materials in terms of structure and how they micellise and to establish whether there are immediate benefits over these gels compared to other polymeric gels such as PEG-PLA copolymer gels and poly(methyl methacrylate) based gels.

5.7 Conclusion

Throughout this chapter the polymerisation methods for producing PLA sodium salts of various polymeric architecture have been discussed. These polymers are all easily reproducible and offer a simple environmentally benign method of making green polymeric surfactants. The next chapter will discuss the physical and rheological properties of these polymers in more depth, with a focus aimed at describing their surfactant, emulsion and thermal properties, how these relate to structure and how altering structure alters the polymer properties.

It has been shown in this chapter that surface active short chain PLA polymers can be prepared without the need for expensive, toxic or air sensitive organometallic or organic catalysts. Although a great deal would have to be improved before these systems could be employed to produce high Mwt (>10,000 amu) PLA, there is room for building upon the results obtained. An area of further study could be in the combining of these shorter chain polymers to produce longer polymer chains containing different amounts of branching. Another area open would be in looking at initiators that could be used to produce cross-linked polymers by radical mediated polymerisation to produce new polymer architectures.

A great deal of further work can be carried out in this area of study with more focus aimed at self assembly of these materials for use in pharmaceuticals or surfactants and the formation of gels that show either hydrophobic or hydrophilic preference with applications in sol-gel chemistry.

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Chapter 6:
Emulsification, Surfactant and Thermal Properties of Polymers where Poly(lactic acid) is the Hydrophobic Chain.

6.0 Aim.

In this final chapter the properties and applications testing of the poly(lactic acid) polymers are discussed in greater depth. To be discussed in detail are:

1) Comparison and reliability study between gel permeation chromatography (GPC) and NMR/MALDI-TOF for polymer analysis.
2) A study of PLA sodium salt surfactants in aqueous media; foaming analysis, methods for determination of critical micelle concentrations, cloud points and DLS for quantifying micellization and aggregation.
3) Emulsification testing using squalane/water and toluene/water mixtures, with reference to non-Newtonian fluids.
4) Thermal characteristics in relation to polymer structure (stereochemistry, initiator and chain length) focus on variations in glass transition temperature (T_g).
5) Thermal decomposition and water uptake studies.

6.1 How Reliable are NMR and MALDI-TOF Compared to GPC?

GPC is considered the primary technique for establishing the mass of a polymer (discussed in chapter 2) and after calibration is considered very reliable. Due to the way that GPC masses are calculated and the way NMR end group analysis works there is usually some small discrepancy between values obtained for number average molecular weight (M_n) using these two methods. Mass spectrometry is not considered a reliable technique for analysis of polymers, even though systems exist that can calculate the M_n and M_w values, because shorter chain polymers are volatilised more efficiently than longer chain ones

End group analysis by ^{1}H NMR spectroscopy can be fairly reliable, although there are several factors that make establishing the M_n value more difficult. In cases where lactide conversion is low, the resolution of the PLA methine protons (main chain peaks) becomes difficult to measure due to overlap with the methine protons of the monomer. For lactide, a quartet is seen at ~5.0-5.17 ppm, for PLA a multiplet of peaks may be observed in the range of 5.18-5.35, making measurement difficult. At very high M_n, the end group peak may be more difficult to observe and integrate, though using higher frequencies for ^{1}H NMR or enhancing the spectrum using a programme such as Topspin works very well.

GPC can also be used to measure the PDI of a given polymer or copolymer and the data obtained can show whether there are competing growth mechanisms as well as how the polymer is distributed. MALDI-TOF can also be used qualitatively to observe the polymer distribution, however it cannot be used to ascertain PDI. It is difficult to obtain the M_w values from MALDI-TOF, as the heavier molecules may not fly and hence will not be detected. With GPC the heavier molecules permeate through the gel faster than the smaller ones, thus providing better resolution for large molecules.

6.1.1 Direct Comparison of M_n Obtained from ^{1}H NMR and GPC.

Table 6.1.1 shows some polymers where the data gathered from the GPC is compared to that obtained by end group analysis using ^{1}H NMR spectroscopy. Many of the results agree well being only a few units out, however there are a few where there are major discrepancies. Below some examples are discussed along with possible reasons for the discrepancy:

Table 6.1.1 Comparison of the M_n values obtained using ^{1}H NMR data and GPC

Name	Ratio (m : i)	M_n (LA units)		MALDI-TOF* (amu)	M_w (amu)	M_p (amu)	PDI
		^{1}H NMR	GPC				
NaPLAB002.2	6 : 1	13	11-12 874 amu	–	1211	1291	1.39
NaLPLAB004.2	6 : 1	13	~ 11 820 amu	–	1149	1246	1.4
NaLPLAB004.11	12 : 1	27	~ 22 1560 amu	1337	2282	2976	1.46
$MeOPEG_{750}LPLA$	20 : 1	38	36-42 3812 amu	–	5270	5136	1.38
ChoLPLAB008	15:1	13	~5 447 amu	969	566	574	1.27
NaPLA B002.11	12 : 1	27	~19 1429 amu	–	2145	2227	1.5
NaHBuALPLA001	6 : 1	13	12 962 amu	–	1347	1409	1.4
NaMandelaLPLAB012	12 : 1	-	19-20 1561 amu	1337	2226	2521	1.43
NaHiVAPLA003	6 : 1	14	9-10 828 amu	–	1175	1225	1.42
NaBHBPLA003	12 : 1	16	24 2359 amu	1395	3398	3661	1.44
NaHHxALPLA002	12 : 1	24	10 852 amu	1425	1169	1246	1.37
KHOctALPLA002	6 : 1	16	14 1212 amu	–	1804	1968	1.49
Na-DL-L-PLAS003	6 : 6: 1	24	18 1303 amu	1553	1996	2391	1.53
Na-L-DL-L-PLAS005	4 : 4: 4: 1	24	15 1125 amu	1193	1575	1770	1.4
Na-D-L-PLA001	6 : 6 : 1	24	18-19 1365 amu	1553	1957	2188	1.43
NaLHiVA-L-D-PLA001b	6 : 6 : 1	19	24 1784 amu	1581	2635	2906	1.48
NaL+DPLAM006	10 : 1 + 10 : 1	19	12-13 927 amu	1481	1376	1538	1.49
NaL+DPLA002	12 : 1 + 12 : 1	28	7-8 597 amu	1409	697	716	1.17

* Predicted M_n value from MALDI-TOF if we assume it is a close approximation to the mean number of molecular weights present.

6.1.2 ChoLPLAB008

Many problems occurred when trying to produce a bulk sample of a choline chloride polymer, especially with L-lactide. The polymer also proved difficult to characterise. There was considerable overlap in the ^{1}H NMR spectrum, therefore the M_n obtained was considered inaccurate. The MALDI-TOF data suggested a short polymer chain with 4-24 LA units.

The end group analysis by ^{1}H NMR spectroscopy suggested a chain length of 13 LA units – which was lower than expected; the GPC analysis gave an M_n value of 4 LA units. There may be several reasons for the major discrepancy in this instance, but it may be linked to the amounts of unreacted lactide and free short PLA chains. Another possibility is the polymer's morphology as a result of interactions with the eluting THF. GPC is also known as size exclusion chromatography, and the idea of size is related to two factors, mass and shape. In most cases the heavier molecules pass through first because they are heavier. However, some heavy molecules cannot pass through easily because of their shape. It is conceivable that, in the case of ChoLPLAB008, there was some micellar formation within the solution that resulted in its inability to easily pass through the gel. It is therefore possible that although these molecules would be larger the micellar shape prohibits them easily passing through he column. However, the MALDI-TOF data, is more consistent with the M_n obtained by GPC, (even though its M_n is larger) but this again could be attributed to micellization leading to poor flight.

6.1.3 Discrepancies with α-hydroxyacid initiated PLA's.

In most of the reactions where α-hydroxyacids were used as initiators a slight discrepancy appears, usually showing larger M_n values obtained through ^{1}H NMR studies. The main reason for these discrepancies comes from free PLA chains that are produced in these reactions, either as a by-product of transesterification or by free hydroxide ROP of lactide. Although acid terminated PLA chains represent a minor product, the ^{1}H NMR experiment cannot make any distinction between PLA attached to the initiator and PLA unattached. Although the GPC does not make these distinctions either, it does analyse by separating out the masses making a more accurate M_n value attainable.

6.1.4 What happens when Polymer is a Gel?

In the case of NaL+DPLA002 the polymer produced was a stereocomplex gel (see Section 5.6.) Comparison between the GPC and ^{1}H NMR spectral analysis shows the largest discrepancy with this polymer; in this instance the GPC is erroneous. The NMR data both for ^{1}H and ^{13}C clearly show a polymer of large molecular weight (by looking at the difference in intensity between chain methine and methine end group protons and carbon atoms). Furthermore, the MALDI-TOF confirms the nature of these long chains.

There is a difference in Mwt of 20 LA units between the value obtained from GPC (7-8 LA units) and that from ^{1}H NMR studies (~28 LA units). The problem in this instance may arise from interactions of the polymer complex with the gel. From previous work it has been suggested that the gel forms as a result of the random orientation of the polymers around each other. These interactions may lead to a polymer arrangement in the THF that is unable to penetrate the GPC gel adequately, resulting in the slow flow rate and lower molecular weight. Good quality polystyrene is used as the standard to calibrate the GPC and works well for linear arrangements of molecules, however if the polymer does not dissolve adequately in the effluent or forms micelles or aggregates, these may not pass through the gel as a result of their shape or insolubility. The former would give the impression that the molecules are lighter than they actually are; the latter once out of solution may not carry to the gel.

Another problem might be loss of polymer through aggregation as it passed through the membrane filter, which is used to prevent contamination by dust or blockage of the GPC syringes etc. This filter will only allow passage of molecules < 50 μm, so aggregates would be excluded from the GPC analysis.

6.1.5 Conclusion

In most cases the GPC results confirm the results obtained by ^{1}H NMR spectroscopy for the M_n values. GPC also provides the polydispersity index, PDI (= M_w/M_n). The PDI gives some idea of how efficient the polymerisations are in terms of molecular weight distribution, which is important in terms of comparing how effective different catalyst conditions are. It would be expected that polymers produced from a lower ratio (L : I) should have a small PDI, and this trend appears to be observed. This suggests that the reaction can be considered a living polymerisation. In a living polymerisation the active chain ends

should be as numerous as the amount of catalyst present, leading to well defined polymer mass and structure.

6.2 Behaviour of PLA Surfactants in Aqueous Media.

When investigating new surfactants there are many criteria that are often studied, these include:

i) Critical micelle concentration
ii) Turbidity
iii) Foaming
iv) Aggregation

All of these factors play an important role in explaining how these surfactants actually work and in dictating their possible uses. Testing these ideas on polyester based surfactants is something of a new area, as little is known about these polymers as surfactants.

The surfactant behaviour of polyesters is relatively unexplored area of research. There are many papers related to copolymers with poly(ethylene glycol), [1] and complex block-copolymers [2] containing both polyester and *n*(oxylene) units, such as *n*-ethylene glycol or *n*-propylene glycol (where n is number of repeat units from 5 – 25). There are few examples of homo-polymer systems that show significant surfactant behaviour.

At the start of this research project, the aim had been to look at PLA as a potential hydrophile, as it had been speculated (by Uniqema) that the polyester groups could have the same sort of aqueous behaviour as the polyether groups in polymers like poly(ethylene/propylene) glycol, which are hygroscopic. However, it has been shown in the previous chapters that this is not the case, as polyesters, especially those of high order, pack too efficiently for water to adequately penetrate the structure and solubilise the surfactant.

The most significant factor for these polymers is the CMC as this relates directly to the turbidity, foaming, surface tension and emulsification. It is by this property that the study of surfactants has become more understood.

6.2.1 Critical Micelle Concentration

Throughout this thesis there has been some discussion of micellization and critical micelle concentration, without much explanation as to what these terms actually mean. Micelle formation is the most important aspect of surfactant chemistry and emulsion chemistry aside from interfacial tension, as the formation of micelles is important in detergency and emulsification. Micelles are self-assembled particles that are forced into a particular orientation through solvent effects.

This self-organisation arises because of the structure of the molecules and how they interact to either maximise or minimise hydrophobic/hydrophilic interactions with the solvents. Most simple surfactants are drawn with a hydrophobic tail and polar head, figure 6.2.1a shows how these molecules can orientate themselves as they assemble under different conditions:

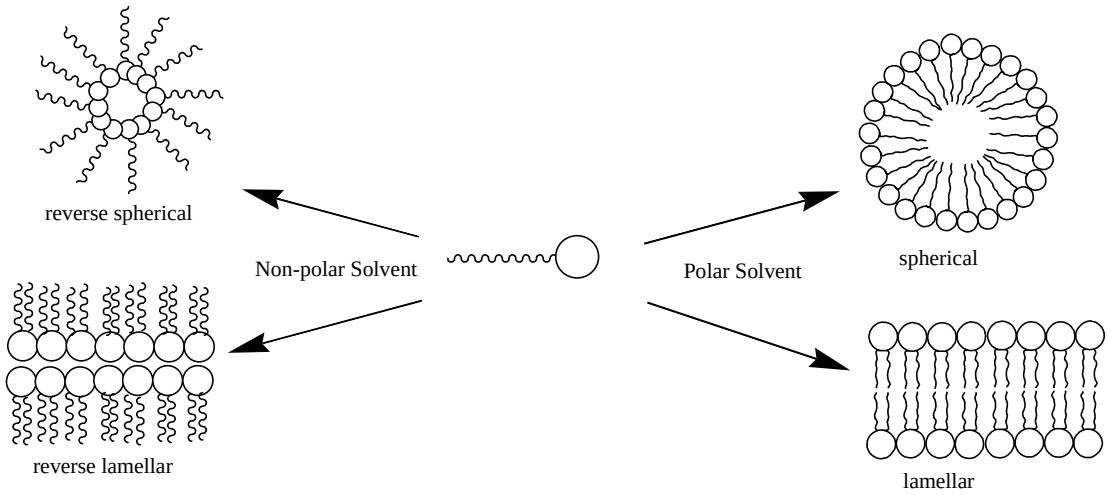


Figure 6.2.1a. Showing how surfactant molecules can arrange themselves into micelles or reverse micelles depending on the nature of solvent.

Micelles are not limited to the shapes shown in Figure 6.2.1a, however; there are various hybrid structures such as cylindrical micelles and aggregates that deviate from spheres, right up to more complicated multicore vesicles (unilamellar and multilamellar) where there may be several layers of molecules.

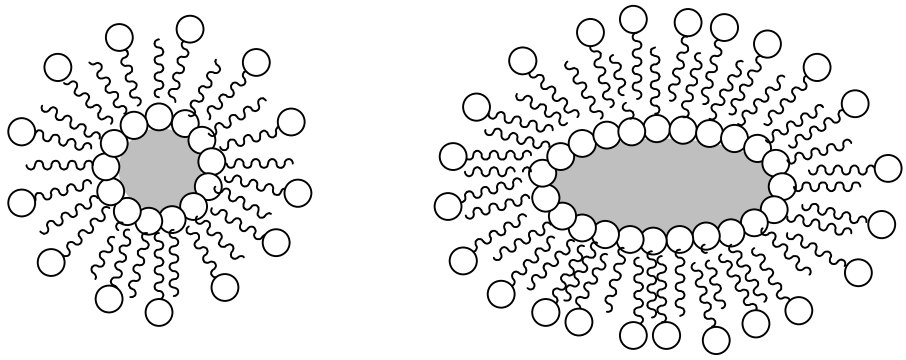


Figure 6.2.1b. Structures of unilamellar vesicles that would be formed in aqueous media. Multi-layer versions are also possible.

The critical micelle concentration leads to a change in the properties of the solution, which can be measured using a variety of techniques such as dynamic light scattering, surface tension or conductivity if the surfactant is ionic. Dynamic light scattering and conductivity are perhaps the most well established methods, as turbidity is related to micellar formation and conductivity changes with surfactant concentration. As the concentration of an ionic surfactant increases, the conductance increases linearly until the CMC, thereafter the rate of increase in conductivity decreases, as shown in Figure 6.2.1c. Similarly, at concentrations higher than the CMC the there is little or no change in surface tension upon further increasing the concentration until after aggregation has occurred.

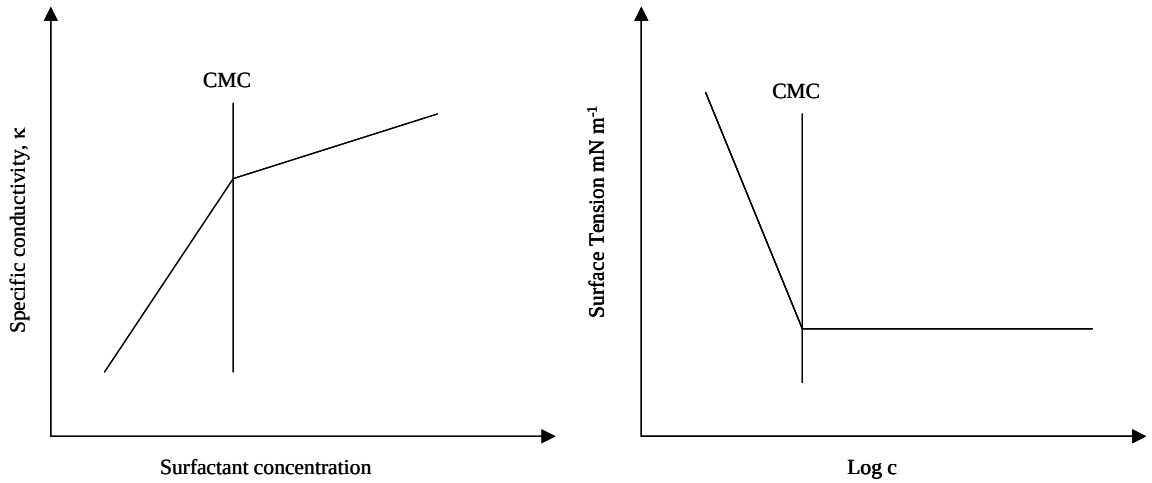


Figure 6.2.1c. Typical plots showing how the CMC may be identified using conductivity or surface tension measurements.

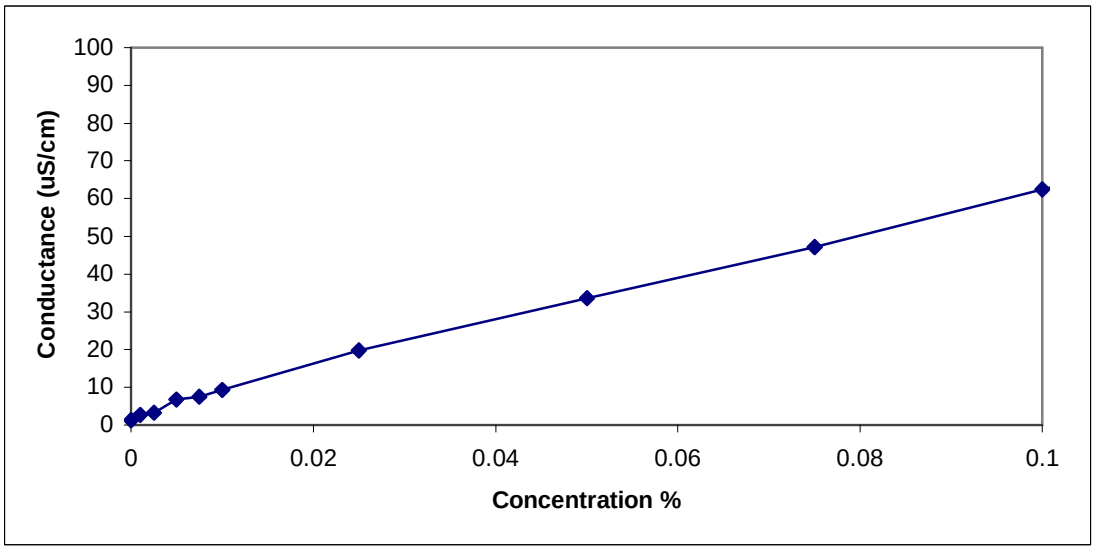
For PLA surfactants the CMC is more related to the hydrophobic tail than the head, as the actual polarity comes about from the anionic end group. The CMC was determined first using conductivity measurements and then by surface tension measurements and compared.

Conductivity is the more reliable method, as the manual tensiometer has no method of controlling water temperature, so there are some fluctuations.

Conductivity Method for determining CMC.

The conductivity method works for all anionic or cationic surfactants since they are conducting species. After the CMC, although the conductance will continue to increase, the formation of micelles reduces the ability to conduct electricity. This is due to fact that un-associated surfactant molecules have both a greater mobility in the solution and dissociate their cations/anions better. When micelles form there is a stabilising effect on the dissociation of the cations and anions as the close proximity of neighbouring surfactant molecules can have counterion effect, leading to ion pairing and a lower intrinsic conductivity. In addition, the large assemblies have a mobility in solution.

A 1 % stock solution was prepared in advance and kept cool to prevent aggregation, then aliquots were taken and diluted to the required concentrations. Approximately 10 cm^3 of the solutions were poured into conical flasks (50 cm^3), clamped in a water bath at 23 ^oC and left for 5 minutes to thermally equilibrate. The conductivity was then measured using a probe connected to a conductivity meter; the probe was washed thoroughly with distilled water and stored in pH 7 buffer solution. Each measurement was repeated 3 times and a graph of concentration vs. conductance was plotted.

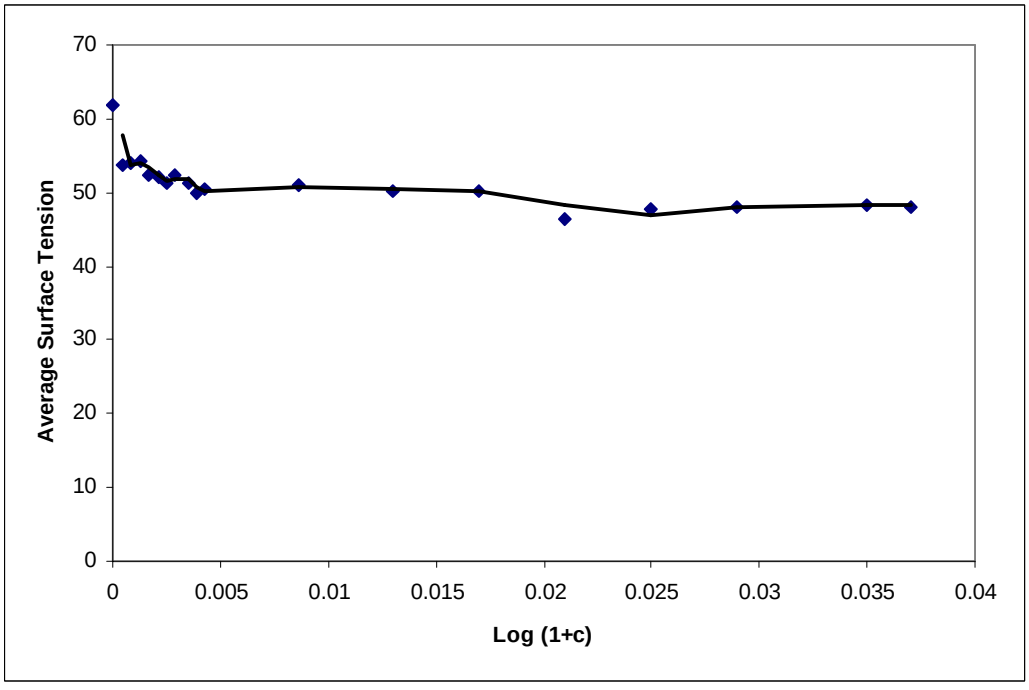


Graph 6.2.1a Shows the plot of conductance vs. concentration.

From the trend line, it appears as though the CMC is approximately at 0.005 %. The M_n of the polymer used was ~940 amu. Therefore the critical micelle concentration for this PLA surfactant is approximately $5x10^{-9}$ mol cm^{-3}. This is reasonable for polymeric surfactants as they have a higher propensity for aggregation and their higher molecular weights compared to traditional C_{12}-C_{20} carboxylates. However looking at the trend line, it would appear that there is another change in conductivity. This is known in some cases to be the result of a change in micellar structure, it is commonly witnessed in alkyl surfactants with chain lengths greater than C_{16} [3]

Surface Tension method for measuring CMC.

Surface tension was also used as a method of determining the CMC for a PLA surfactant. There are many problems inherent with this method as temperature cannot be easily regulated, and changes in surface tension before and after the CMC are often far smaller than the change in conductance. However, the surface tension method was used to calculate the CMC for a KHHxAPLA polymer with M_n ~ 1700 amu (almost double that of the sample used for conductivity). From the graph in Figure 6.1.2c, the CMC occurs at approximately 0.005 % (50.56 mN m^{-1}). This translates to a CMC of $2.9x10^{-8}$ mol cm^{-3}.

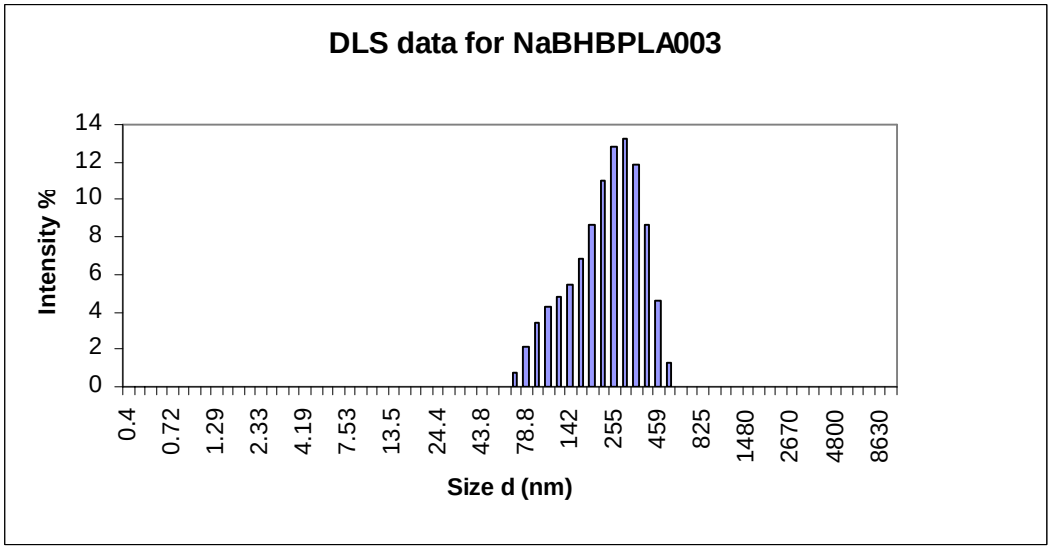


Graph 6.2.1b Shows a plot of Average surface Tension against log of concentration.

Hydrodynamic Radius of Micellar Particles obtained using DLS.

Using dynamic light scattering techniques it is possible to obtain the hydrodynamic radius of micelles and vesicles (as was explained in Chapter 2). The size of the particles can give information as to self-assembly characteristics of the solution and all solutions were prepared above the CMC. 1 mg cm^{-3} solutions were prepared, initially passed through a membrane filter or filtered through glass wool to remove dust and other large particles prior to the measurement. The DLS data was recorded and graphs were produced showing the average particles sizes.

The following graph shows the DLS distribution for a sodium BHB initiated polymer, the average hydrodynamic radius is 251 nm. The distribution of the graph shows a range of sizes for the micelles, from 68 nm to 531 nm.



Graph 6.2.1c Graph showing size distribution in DLS plot.

The data in table 6.2.1 was all taken on the same day. The solutions were prepared and measured within a 20 minute window, as larger aggregates will form on standing even at ambient temperature over prolonged periods.

Table 6.2.1 showing the hydrodynamic radius compared to the M_n values and PDI of the polymers.

Name	Ratio (m : i)	M_n		M_w	PDI	Hydrodynamic Radius (nm)
		^{1}H NMR	GPC			
NaPLAB002.2	6 : 1	13 LA	~ 12 LA	1211	1.39	96
NaLPLAB004.2	6 : 1	13 LA	~ 11 LA	1149	1.4	121
NaLPLAB004.11	12 : 1	27 LA	~ 22	2282	1.46	158
$MeOPEG_{750}LPLA$	20 : 1	38 LA	3812	5270	1.38	194
ChoLPLAB008	15:1	13 LA	447	566	1.27	213
NaPLA B002.11	12 : 1	27 LA	~19	2145	1.5	181
NaHBuALPLA001	6 : 1	13 LA	962	1347	1.4	249
NaMandelaLPLAB012	12 : 1	-	1561 19-20 LA	2226	1.43	237
NaHiVAPLA003	6 : 1	14 LA	828	1175	1.42	165
NaBHBPLA003	12 : 1	16 LA	2359	3398	1.44	251
NaHHxALPLA002	12 : 1	24 LA	852	1169	1.37	288
KHOctALPLA002	6 : 1	16 LA	1212	1804	1.49	362
Na-DL-L-PLAS003	6 : 6: 1	24 LA	1303	1996	1.53	248
Na-L-DL-L-PLAS005	4 : 4: 4: 1	24 LA	1125	1575	1.4	334
Na-D-L-PLA001	6 : 6 : 1	24 LA	1365	1957	1.43	312
NaLHiVA-L-D-PLA001b	6 : 6 : 1	19 LA	1784	2635	1.48	332
NaL+DPLAM006	10 :1 + 10:1	19 LA	927	1376	1.49	179
NaL+DPLA002 (gel)	12 : 1 + 12 : 1	-	597	697	1.17	610

The first suggestion that larger aggregates formed within a relatively quick timeframe came from the observation that the membrane filters (50 μm pores) had become clogged – indicating the presence of predominantly larger micelles. Where this was the case, the solutions were filtered through a glass-wool plug in a Pasteur pipette. NaPLAB002.2 and NaLPLAB004.2 were tested again after a 24-hour period to ascertain how much the average hydrodynamic radius had changed. For B002.2 the hydrodynamic radius had doubled from 96 nm to 184 nm and for B004.2 the size had more than trebled from 121 nm to 384 nm. There were also traces of larger sediment and aggregates that were removed when filtering. These observations provide a good indication that L-PLA chains show a greater propensity for micelle and aggregate formation, and may form larger and more stable micelles than D,L-PLA chains.

6.2.2 Does Cloud Point Relate to PLA?

There is a phenomenon often observed for poly(ethylene oxide) surfactants (also called polyoxyethylenated or POE surfactants) known as the cloud point. The cloud point [3] is the temperature at which the solution becomes turbid and above which two phases may form. It is observed for POE surfactants when the hydrophilic portion is less than 80 % of

the molecule, and occurs through the formation of larger spherical micelles, which show increased intermicellar attractions.

This behaviour has proved important for the biomedical applications of PEG copolymers as they form large multi-core micelles that can be used for drug delivery purposes. It is also related to the sol-gel behaviour of these copolymers. Cloud point phenomena do not however, occur for polyester or ionic surfactants. The PLA based surfactants we have synthesised have shown an increase in turbidity with time and temperature and the reasons for this occurrence can be similar to those for polyethers. Cloud point is considered to occur as a factor of hydrophilicity of the molecule, but PLA based hydrophobicity allows for some hydrophilic interaction. It is conceivable that PLA based surfactants, like PEG based surfactants can be considered to have a 3-part surfactant with a hydrophobic middle section (the main chain) and two polar head groups, one of these being very polar ($-CO_2^-$ and one slightly polar (C-OH).

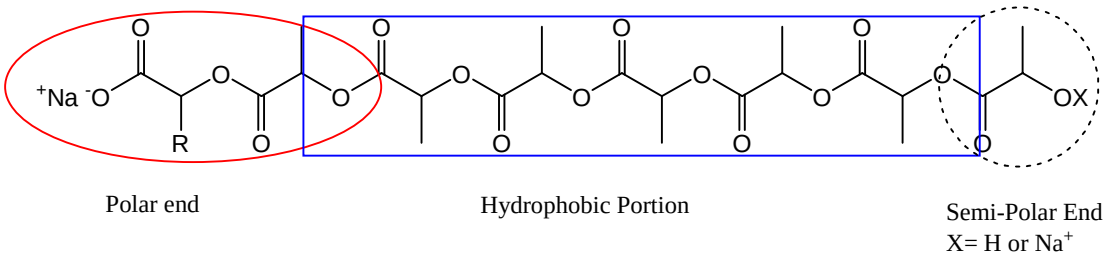


Figure 6.2.2a Showing areas of likely hydrophile/lypophile interaction.

These polymers show cloud point behaviour. To measure cloud point behaviour in a sodium PLA surfactant, solutions (1 mg cm^{-3}) were prepared and heated in a water bath until turbid. The point of turbidity was taken as the time taken until a marked point became obscured. The photographs in figure 6.2.2b show an experiment with a 12 : 1 (lactide : sodium lactate) ratio polymer. Immediately after preparing the solution there is some cloudiness. However at room temperature (23 ^oC) the measuring point did not become obscured for 87 minutes. Like other cloud point surfactants the rate at which turbidity occurs increases with temperature.

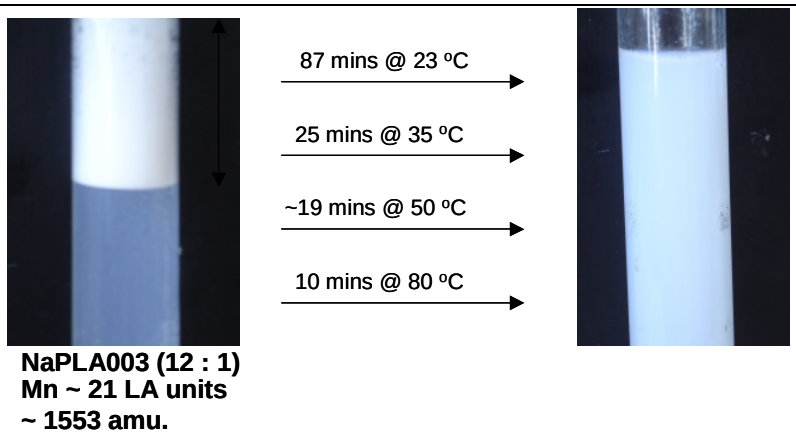


Figure 6.2.2b Photographs showing the change from cloudy to turbid. The picture on the LHS shows the solution + the foam it produced, and the RHS shows the turbid solution.

Although a phase change was not recorded in these samples, for other samples that have been stored at room temperature over several weeks, a phase separation has been observed. Figure 6.2.1c shows a photograph of a sodium BHB initiated sample that shows some phase change behaviour, this has occurred to higher aggregates. Looking at the picture carefully it can be noted that there is a purely aqueous phase above that of a concentrated solution phase, which contains well-dispersed aggregates. Similar observations have been made with POE based surfactants.

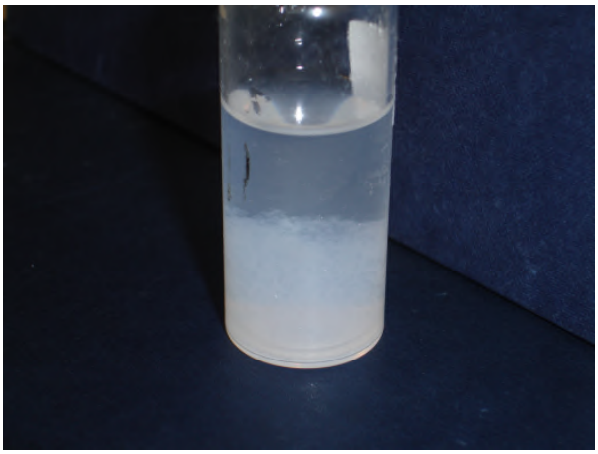
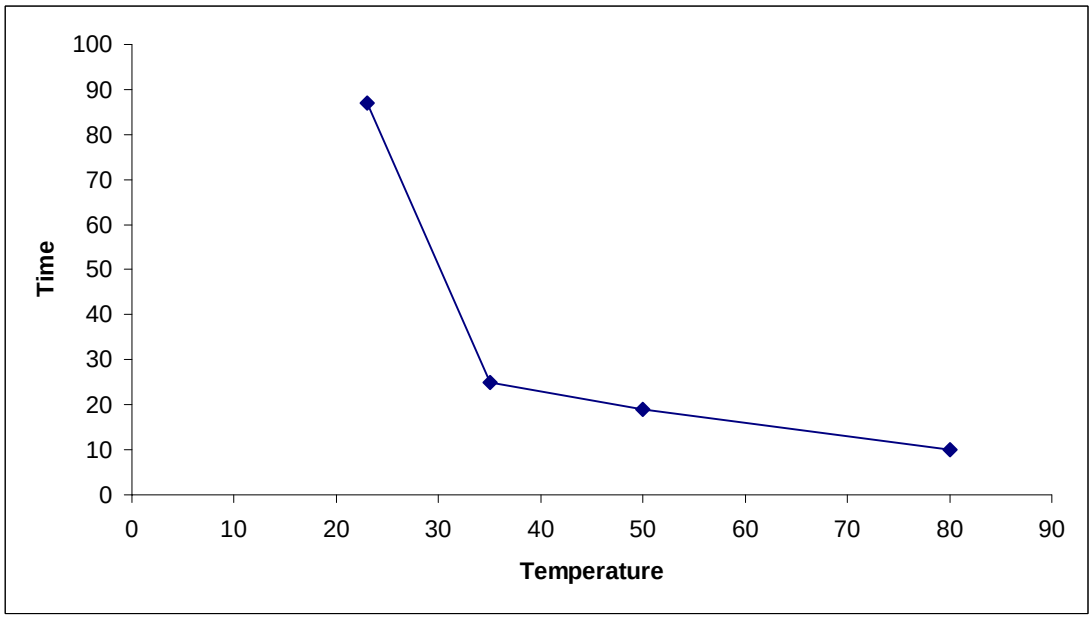


Figure 6.2.2c A photograph showing phase separation in a NaBHB based surfactant after 1 month.

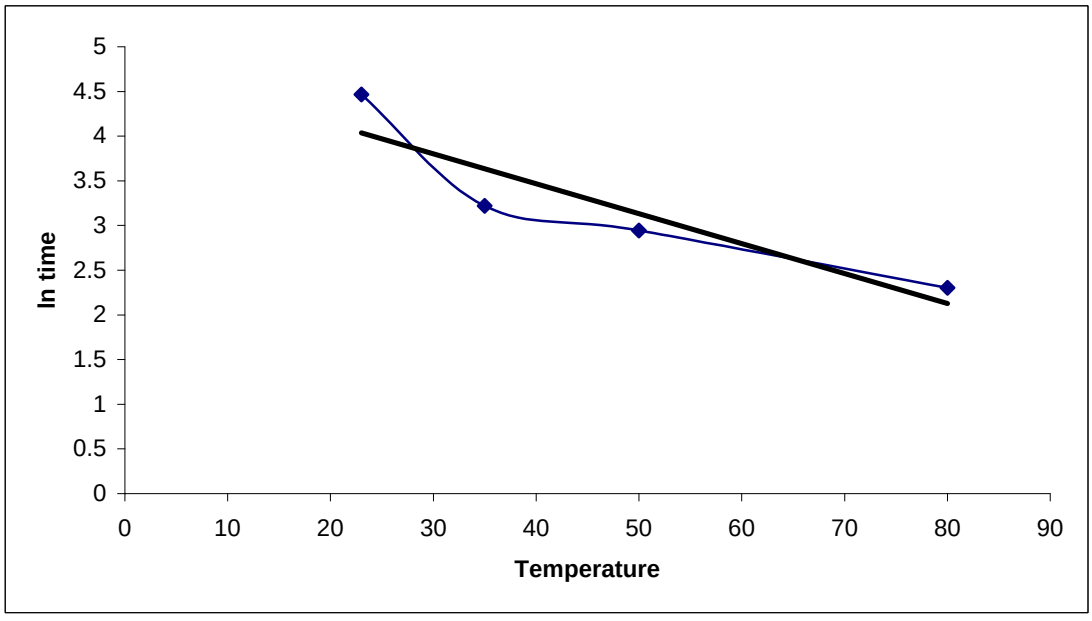
Graphs 6.2.2a and 6.2.2b show the turbidity as a function of temperature and time. The almost linear plot of ln time vs. temperature, suggests an exponential relationship, of the form:

$$t=Ae^{-T}$$

where t is time, A is a constant and T is temperature.



Graph 6.2.2a Shows the relationship between temperature and time for the solution to become turbid



Graph 6.2.2b Data from Graph 6.2.2a plotted as a ln(t) vs T plot

The graph of ln(t) vs. T is fairly close to linear. This could perhaps be made clearer by taking more data points in the middle of the reaction, however, there is an upper and lower threshold regarding temperature as a) water is the solvent and b) the solubility of the polymer is reduced in colder water.

From the above there is compelling evidence that PLA sodium salts can be viewed as similar in nature to POE non-ionic surfactants and could lead to further developments in the study of PLA and other esters as the hydrophobic portions of surfactants. That the observed surface activity leads to interesting emulsification behaviour for NaPLA with viscous organics, which will be discussed in a later section.

6.2.3 Foaming.

Foaming is an important characteristic of surfactants, as it may or may not be desirable depending on the applications. Foaming is related in part to the critical micelle concentration of the surfactant, but cannot be used to quantify it, as the maximum foam height may be above the CMC. A low CMC surfactant usually makes the better foaming agent.

Foaming is caused by the trapping of air in micelles, leading to a liquid-air, low-density colloid that travels up to the surface. Surfactants that lower the interfacial tension of the water aid foaming. At the surface, lamellar micelles of the form liquid-air-liquid form and may also merge to alter the micellar shape; i.e from spherical to polyhedrons. The eventual breakdown of the foam occurs due to gravity, as the liquid breaks the surface of the micelle and returns to the water phase.

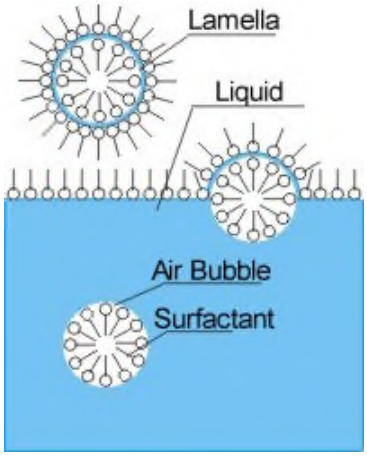


Figure 6.2.2 Shows the formation of spherical and lamellar micelles in a surfactant solution [4].

The most important characteristics of foaming are foam height and foam stability and there are a few established methods for quantifying these. The two most common methods employed are the Ross-Miles [3] method (liquid drop method) or a method where gas (air or N_2) is bubbled through the solution at a constant rate. The initial foam heights are recorded

and then the foam height is compared to that taken a short time later (3 minutes). The foam stability can be calculated from these methods.

For quantifying the foaming of PLA sodium salts the surfactant quotient was used initially. Initially it was developed to assess whether the surfactant a) dissolved and b) was surface active. If the polymer was insoluble then there was no point measuring its surface tension as the Wilhelmy plate method cannot work when aggregation has occurred.

Later a quick study of foam height and stability was carried out using a selection of 12:1 ratio surfactants (1 mg cm^{-3}). A simple shaking method was used to determine the foam height. Polymer (25 mg) was transferred to a 50 cm^3 measuring cylinder and distilled water (25 cm^3) was added. A rubber septum was placed on top of the measuring cylinder and the polymer solubilised in the sonic bath for 10 minutes. The solution was removed and shaken rigorously for 1 min. The foam height was recorded and foam stability checked after a further minute. Foam stability is taken as the time taken for the foam to settle/break.

Results:

Table 6.2.3 Data on foam height and stability for a number of Poly(lactic acid) sodium salts.

Lactide	**Initiator**	**M_n (LA units)**	**Surfactant Quotient**	**Initial foam volume cm^3**	**Foam stability cm^3**
L	GHB	28	5		
D,L	NaHiVA	26	4.5	3	1
L	NaHiVA	24-25	5	5	1
D,L	KHHxA	22-23	5	5	2
L	KHHxA	26-27	5	6	2
D,L	NaBHB	5-6 per arm	5	23	12
L	NaBHB	11 per arm	5	8	4
D,L	NaMan	25	4	4	2
L	NaLMan	22	4	7	4
D,L	KHOctA	24	3	1	0
L	KHOctA	_	4.5	4	2

There are several trends that can be seen from the data in Table 6.2.3. For example, L-PLA seems to produce more stable foam than D,L-PLA. What is most interesting to note is that the most actively foaming and stable surfactants were the NaBHB initiated polymers, this is as a result of the surfactant structure. In the previous chapter it was noted that the BHB

molecule was unique among the initiators used as, being a β–hydroxyacid, it has the ability to rotate around at the BHB-PLA arms, allowing the maximisation/minimisation of hydrophilic interactions. In this case the polymer maximises the hydrophilic interaction, creating a head with two tails. Where two heads are often better than one, this is also the case for surfactants with two tails. It is well documented that surfactants that deviate from molecular linearity are show higher initial foaming [3]. The more stable foam results from an increase in interchain interactions in the form of the micelle. Two tails leads to an increase in the electrostatic cohesion that already exists between the polyester molecule, however the reason why this molecule is likely to be a better foaming surfactant is that the resulting micelles from this polymer could be considered more porous (or have larger channels) and able to hold air and water better leading to an increase in foam height and stability.

6.2.4 Aggregation.

It is generally accepted that as the chain length increases and the molecules tend towards greater hydrophobicity there is a higher propensity for micelle formation and aggregation. The reasons for aggregation are two fold and in part also relate closely to foaming ability. Above the CMC most of the surfactant exists in the form of micelles or vesicles and over time and temperature these particles may continue to grow until they are no longer water-soluble or dehydration within the core of the micelle/vesicle takes place (like when foam collapses). Aggregation can occur as the expansion of micelles or by the coalescence or coagulation of micelles.

PLA based surfactants appear to have a high propensity towards aggregation – due to the long chain length and strong interchain interactions. In PLA surfactants aggregation can take many forms. One has been described in terms of cloud point, but several other forms of aggregation have also been witnessed. These have been termed powdering, gelling, surface aggregation and suspension.

Figure 6.2.4 shows how the micelles can arrange to form a particular type of aggregate, the actual behaviour is probably much more complicated with much larger micelles forming in some cases as well as the micelles coalescing.

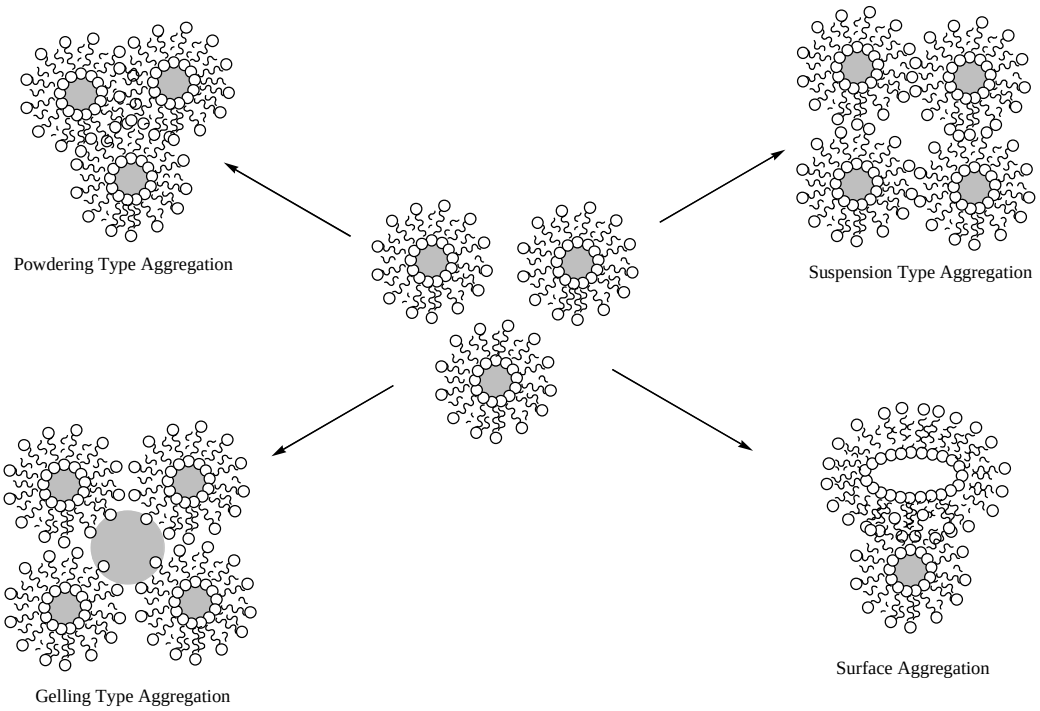


Figure 6.2.4 Shows aggregation as micelles interact in aqueous media.

The following phenomena have been observed in either normal shake tests or when highly concentrated polymer solutions were prepared for TGA analysis, which will be discussed in a later section.

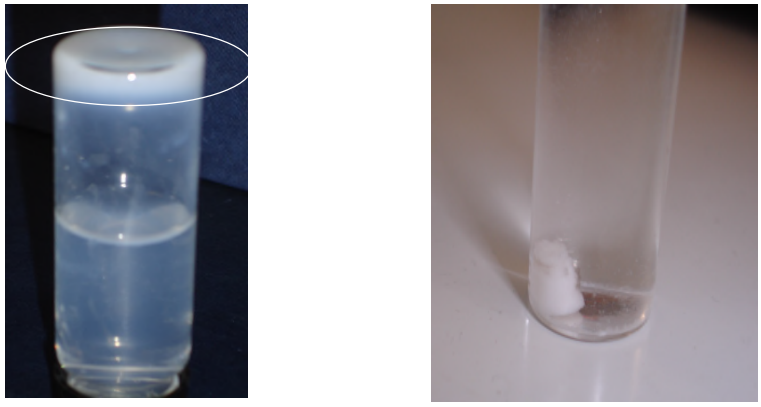
Powdering

Powdering is the most common form of aggregation that is witnessed with PLA surfactants. With powdering the surfactant initially dissolves producing good foaming activity and typical surfactant behaviour. Over time the solution becomes more turbid (discussed in cloud point) (1-2 hrs at RT) before some of the surfactant precipitates as a powder at the bottom of the vessel. This powder may or may not be re-solubilised in water, but upon re-shaking the solution retains its surface-active ability, and shaking the solution independently of the powder in another vial also shows surfactant activity.

Gelling

Gelling is one of the less common forms of aggregation that is seen. In gelling the polymer solution, after shaking, settles and eventually forms a gel. In some cases the gel will dehydrate and shrink over time into a polymer pellet.

The dehydration phenomenon is interesting, as it has only been recorded for one type of polymer at high concentrations. The polymer with prefix M005 was a test sample prepared by mixing two polymers of approximately the same M_n and the same stereochemistry, as both chains were produced from racemate. Here the polymer formed a gel that over time continued to shrink to form a pellet that retained the cylindrical shape of the container (see Figure 6.2.4b).



Gel formation Dehydrated gel, forming pellet

Figure 6.2.4b Pictures show the formation of polymer gel and pellet.

Surface Aggregation

Surface aggregation occurs when the average chain length exceeds ~ 27 LA units and when long branched initiators such as KHOctA and KHHxA are used as initiators. In surface aggregation the surfactant solutions, once formed or partially formed by sonication, show some surfactant ability, but on the breaking down of the foam, aggregates form on the surface. These aggregates never re-dissolve and there is no further foaming action. Once the air trapped in the micelles escapes they sink to the bottom of the vial. The foaming ability and surface tension cannot be measured for these surfactants. Part of the problem here may arise from the inaccessibility of the cation, which reduces the overall surfactant behaviour.

6.2.5 Conclusion

The aqueous chemistry of PLA based surfactants shows complex behaviour, from pseudo cloud point behaviour in BHB initiated polymers to large aggregates and dehydrating gels. This propensity for aggregation is probably in part responsible for a range of other properties such as emulsification and thermal stability, which will be discussed in further sections.

6.3 Emulsification in Water/Organic Media.

Emulsification is an important property of some surfactants. An emulsion is formed when two immiscible phases are mixed together in the presence of an agent that can break the surface tension of both media. To form an emulsion, one of the liquid phases forms droplets, which are suspended in the other phase; whether an oil in water emulsion (O/W) or a water in oil emulsion (W/O) forms depends on the emulsifier used. There are few emulsions that form without the presence of an emulsifier, though many natural emulsions are known, such as milk (emulsion and dispersion). Emulsions find a wide range of applications in both personal and industrial applications:

1) Personal care and medical applications such as creams and lotions.
2) Food products such as margarine
3) Industrial applications such as drilling muds
4) Research applications such as in emulsion polymerisations, emulsion catalysis.

There are several types of emulsion which give rise to different behaviour. Emulsions can be broken down into 3 basic types [3]. Macroemulsions are the most common type where the emulsion particles are >400 nm and are visible under a microscope. Microemulsions with particles between 100 nm and 400 nm provide *transparent* dispersions – usually with a blue/white hue. Multiple Emulsions – emulsion within an emulsion – can also occur.

All the emulsions made using PLA sodium salts can be considered macroemulsions, although the behaviour may be more complex and veer towards multiple emulsions. In a macroemulsion there are two possible dispersed phases O/W and W/O, using the Bancroft rule it is possible to predict which will form based on the hydrophobicity/hydrophilicity of the emulsifier. Generally, if an emulsifying agent is more water-soluble, it will form O/W emulsions and vice-versa. It is possible to inverse some emulsions by altering the physical conditions.

There are relatively simple ways to ascertain whether an emulsion is O/W or W/O. The first method is to take some of the emulsion and put it in a sample of water. An O/W emulsion will be easily dispersed whereas a W/O emulsion will not. This is because an emulsion can only be readily diluted with whatever medium makes the outer phase of the emulsion particles. Another simple test is to use cobalt (II) chloride papers. Cobalt (II) chloride is used as dyestuff in drying agents (such as drierite) as the hydrated salt and dehydrated salts have strong colour difference, the dehydrated salt is deep blue and the hydrated salt is pink. When a W/O emulsion is dropped onto the paper, as the drop spreads out it will leave a pink core with a blue corona (as the oil spreads), if the emulsion is O/W the core will remain somewhat blue but a wide pink corona will form as the emulsion spreads out. The pictures below show the characteristics seen when an emulsion is O/W and W/O:

Pink colour indicates O/W emulsion.

Pink centre surrounded by blue indicates W/O emulsion.

Figure 6.3. Pictures showing a distinction between O/W and W/O emulsions.

6.3.1 Water/Squalane Emulsions

Squalane is a common oil used to test emulsifiers. As it is a long chain branched hydrocarbon (2,6,10,15,19,23-hexamethyltetracosane; $C_{30}H_{62}$) it is a very low miscibility in water and thus only the most rigorous of emulsifiers will work. Squalane is a naturally occurring oil, which, as well as being produced in human skin by the sebaceous glands, is commercially sourced from the livers of shark species (Japan) and olives (Europe) and is a high value chemical used in a wide variety of skin-care applications.

For PLA based emulsifiers an overall concentration of 2.5 mg cm^{-3} was used and water/squalane ratios of 1:1 and 3:1 were principally employed. The surfactant was dissolved as much as possible in water using sonication before the squalane was added. It was re-soniccated after the addition of squalane. The solutions were then shaken vigorously for 1 minute and allowed to stand for 1 minute initially. The time taken for the emulsion to break was recorded. What was quickly noted with NaPLA surfactants was that with squalane they showed thixotropic behaviour. From this point the emulsion tests became focussed on how much time was required to reach thixotropy as well as breaking.

Thixotropy or shear thinning is a known phenomenon in emulsion preparation. Thixotropic phenomena first came to the forefront of scientific discussion in the 1930's in a paper by C.F. Goodeve [5]. In thixotropic emulsions once the emulsion is allowed to settle there is an increase in viscosity, often to the point of gelling. When the emulsion is re-shaken the viscosity decreases. The changes in viscosity are attributed to many factors, such as the shape of micelles and the reorientation of the emulsion particles. In PLA based surfactants the viscosity changes are largely the result of an increase in interparticle interactions – occurring when the emulsion is at rest. What also seems to have an effect is, that, in most cases, not all water is taken into the emulsion phase seems also to be important. Therefore it stands to reason that thixotropy occurs at the point when an specific ratio of water : oil is reached, i.e. water in an O/W emulsion collapsing back into its own phase would lead to stronger interactions between emulsion particles as the dispersion volume is effectively reduced.

With a more water-soluble polymer – it should be that the emulsion formed is O/W. However, this is not always the case! In many cases where water breaks from the thixotropic

phase the top phase of the emulsion is shown to be W/O. This leads to the scenario where thixotropy probably occurs by inversion of the emulsion. In some cases two emulsion phases are seen where there is a O/W emulsion on the bottom and a W/O emulsion on top – this may be because of the polydispersity of the polymers used, i.e. shorter polymer chains are more soluble in water and longer polymer chain ones are more organic phase soluble. The PLA surfactants are insoluble in neat squalane and therefore can only be used when dissolved in water first.

6.3.2 Thixotropic Emulsions and Emulsion Stability.

To test if an emulsion is thixotropic there are many methods that may be employed. These include measuring the shear viscosity using a rheometer, or turax. Due to limits with equipment there is a method commonly applied for analysis of sol-gel materials, that can be modified to look at emulsions [6]. The tilt method requires no expensive equipment only a dedication of time. In the tilt method the emulsion after shaking is left to stand for an allotted period of time it is then tilted 90^{o}, then 180^{o}. If the emulsion does not collapse or spill then it is considered thixotropic. If it spills the vial is re-shaken for 1 minute and left. The time taken for the emulsion to become thixotropy or to break is recorded in tables 6.3.2a, 6.3.2b and 6.3.2c.

Table 6.3.2a Thixotropy Data for PLA emulsions

Polymer	Water:Squalane Ratio	M_n (LA units)	Time to Thixotropy (minutes)	Time to Breaking (minutes)	Water Separation (mm)
NaMandelaLPLA002	1 : 1	17	8	_	1
NaHHxALPLA001	1 : 1	7	90	_	10.5
NaHHxALPLA002	1 : 1	24	< 1	_	0
NaHHxAPLA001	1 : 1	10	8	_	7*
NaHHxAPLA002	1 : 1	16	_	3	_
NaHiVALPLA001[a]	1 : 1	17	8	_	11 after 1 hr
NaHiVALPLA001[b]	1 : 1	9	25	_	8
NaBHB003	1 : 1	8 per arm	2	_	0
NaHiVALPLA002	1 : 1	13	< 1	_	0
NaLPLAB004.2	1 : 1	13	10	_	4
NaHBuAPLA002	1 : 1	21	_	< 1	5 mm squalane
NaBHBLPLA001	1 : 1	6 per arm	8	_	b
NaManPLA001[c]	1 : 1	16	60	80	c
ChoLPLAB008	1 : 1	16	30	_	6
NaManLPLA001	1 : 1	13	_	4	_
NaHiVAPLA003	1 : 1	14	2	_	0
NaHiVAPLA004	1 : 1	28	4	_	0
NaPLAB002.11	1 : 1	26	2	_	14
NaBHBLPLA002	1 : 1	6 per arm	_	10	_
NaHBuALPLA001	1 : 1	25	30	_	15
NaGHBuAPLA001	1 : 1	14	_	30	_
NaLHiVALPLA001	1 : 1	18	6	_	0
NaLHiVAPLA001	1 : 1	18	_	30	_
NaHiVADPLA001	1 : 1	14	4	_	0
KHOctAPLA001	1 : 1	15	_	60	_
KHOctALPLA002	1 : 1	16	6	_	0

* After 2 days the water layer had further separated to 12 mm (~5 cm^3); [a] Forms two emulsion layers W/O upper phase and O/W lower phase; [b] Eventually formed two emulsion phases but retained thixotropy; [c] forms two phases, the upper phase breaking after 80 mins, but the O/W phase remains stable.

1 : 1 Water/Squalane ratios generally show good thixotropic properties and generally L-PLA chains result in better emulsification properties than D,L-PLA chains, although exceptions such as the NaBHB initiated polymers exist. Here emulsion stability may be attributed to the shape of the surfactant molecule, which can arrange to minimise or maximise

hydrophilic/hydrophobic interactions. The photos below illustrate the emulsion and thixotropic properties of water/squalane emulsions at 1 : 1 ratio.

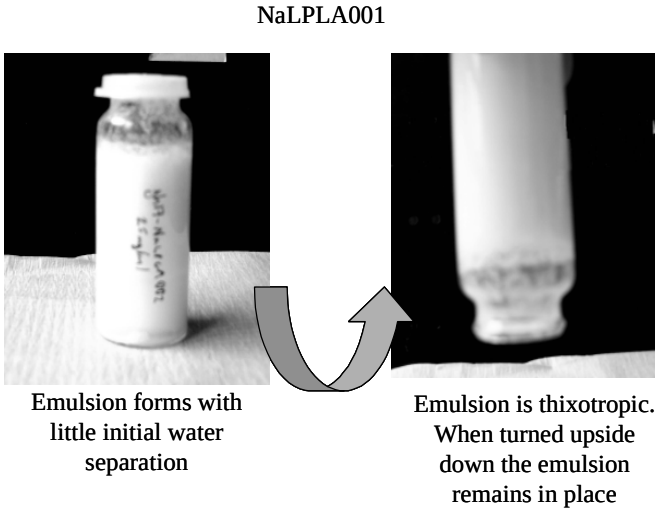


Figure 6.3.2 Photographs showing the thixotropic nature of PLA based surfactants at a 1 : 1 ratio of water/squalane, as the emulsion is left to stand it thickens, when shaken (sheared) returns to liquid.

Table 6.3.2b Shows the data on thixotropic emulsions formed with water/squalane emulsions, relating closely the M_n to thixotropic performance.

Polymer	Water:Squalane Ratio	M_n (LA units)	Time to Thixotropy (minutes)	Time to Breaking (minutes)	Water Separation (mm)
NaMandelaLPLA002	3 : 1	17	14	_	7
NaHHxALPLA001	3 : 1	7	_	60	_
NaHHxALPLA002	3 : 1	24	40	_	3
NaHHxAPLA001	3 : 1	10	2	_	32
NaHHxAPLA002	3 : 1	16	_	0	_
NaBHBLPLA001	3 : 1	6 per arm	_	_	a
NaManPLA001	3 : 1	16	_	90	_

a) Eventually formed two emulsion phases but retained thixotropy.

3 : 1 (water : squalane) emulsions were tested as this is a common ratio used for emulsification purposes for PLA surfactants. However, they do not form stable or thixotropic emulsions. There is no adequate reason why 3 : 1 should be poorer than 1 : 1, the reason may be that where strong emulsification occurs the polymers are at a concentration where aggregation also occurs. It is possible that, although the polymers are not wholly soluble in water (at this concentration) and are insoluble in the presence of only squalane; the water

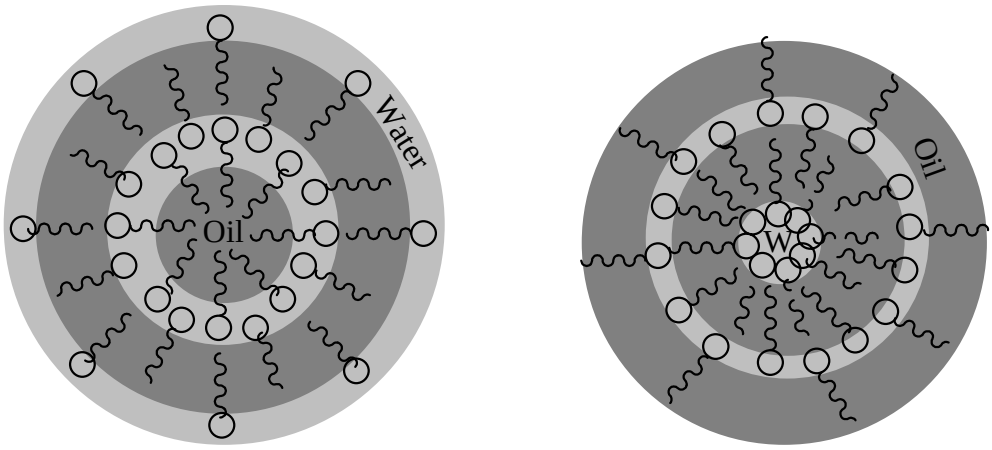
causes the polymer chains to re-orientate to the point where the oil is able to penetrate i.e. the water solubilises the polymer in the oil. This would account for the overall solubility and emulsification behaviour of the systems. It is therefore conceivable that at the 3 : 1 ratio the initial concentration of surfactant is too low and, in order to form the emulsion, a higher volume of oil is required. If the chain lengths of the polymer are considered using the Bancroft Rule, then the polymer should be more oil soluble thus favouring W/O emulsion.

Table 6.3.2c Shows the data on thixotropic emulsions formed with water/squalane emulsions, where polymer stereoblocks or blends were used as emulsifier.

Polymer	**M_n (LA units)**	**Time to Thixotropy (minutes)**	**Time to Breaking (minutes)**	**Water Separation (mm)**
Stereoblocks:				
NaLHiVA-L,D-PLA001	26	3	_	5
Na-D,L-PLA	24-25	< 2	_	2
NaD,L-L-PLAS003	24	2	_	0
NaL-D,L-PLAS004	27	6	60	0
NaL-D,L-L-PLAS005	24	2	0	9
Polymer Blends:				
NaLHiVAL+DPLA001	19	10	_	0
NaD,L+D,LPLAM004	19	_	6	_
NaD+LPLAM006	19-20	6	_	6

All Thixotropy measurements were taken at a 1 : 1 water : squalane ratio.

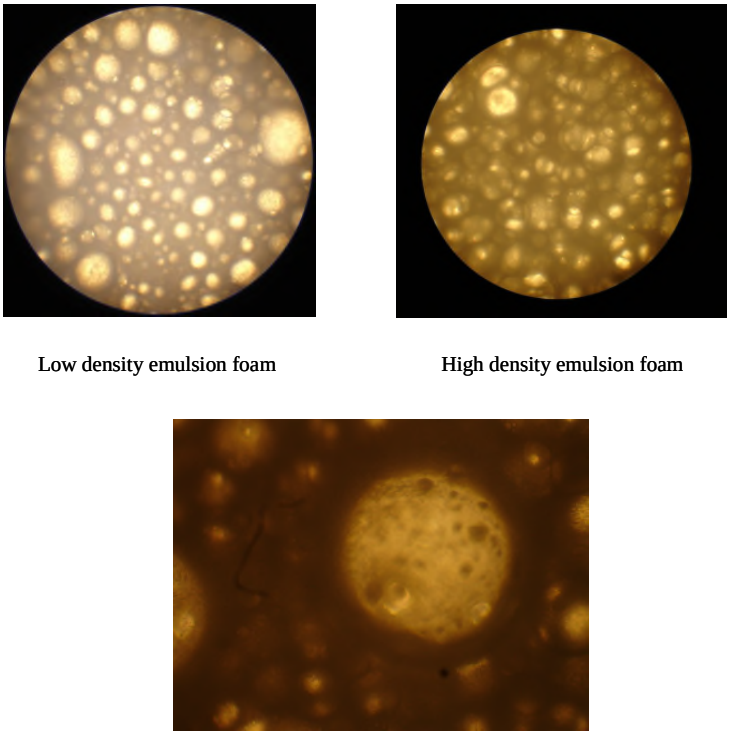
A combination of stereochemistry and chain length seem to be the overriding factors in determining emulsification and thixotropy. In Squalane based surfactants where emulsions are formed, they are almost always thixotropic and many of them are stable for months. Looking at the stereoblocks and blends confirms that stereochemistry is important. The best results are obtained were the polymers contained isotactic blocks, and, where there were D,L-PLA blocks, thixotropy depends largely on position. If the D,L-blocks are at the end of the chain, this produces a less stable emulsion than if an L or D block is at the end. However, whether the D,L block is in the middle or at the beginning makes little difference, suggesting that the key to thixotropy lies with the ability to pack at the tail of the molecule. This makes sense, if we consider that, in an emulsion the micellar type structure would be multi-lamellar (vesicle), and, if spherical would be as in Figure 6.3.2:



O/W Emulsion Sphere W/O Emulsion Sphere

Figure 6.3.2a Multilamellar emulsion spheres, showing W/O and O/W emulsion particles.

Looking at the polymer blends suggests that they are able to emulsify squalane but have no real advantages over normal polymer systems. Using an ordinary microscope at x10 to x20 magnification it was possible to see the emulsion spheres formed. The photographs below (figure 6.3.2b) were taken from a NaHHxA emulsion and show the particles both from a dense portion and more dilute portion of the slide, as well as a close-up of an emulsion sphere.



Low density emulsion foam High density emulsion foam

Close up of one of the emulsion spheres

Figure 6.3.2b Photographs of a NaHHxA emulsion.

6.3.3 Water/Toluene Emulsions.

In line with the methods set out by Uniqema/Croda to test emulsions, this series of experiments took place at Nottingham University under the supervision of Prof. Derek Irvine and Dr Kristofer Thurecht. Most emulsification testing carried out in commercial labs, uses high shear mixers to produce emulsion solutions as they ensure an even dispersion of polymer throughout the emulsion and maximise water/organic interactions.

At Nottingham there was access to a Silverson high shear mixer, which has a shear rate up to ~11000 rpm. Where initially Uniqema had suggested using squalane or another high viscosity oil, Croda recommended using toluene and produced a protocol for these tests. These results for toluene/water emulsions vary greatly from the squalane/water emulsions, as the oil (toluene) is now the better solvent for the polymer; this in part may account for the very different emulsification behaviour that has been observed.

Procedure:

A 10% solution of the polymer in toluene was prepared so that the overall concentration in the emulsions would be 2.5 % (w/w). Due to the heat produced by the high shear mixer all emulsification tests were carried out using an ice-bath to reduce toluene evaporation, which would cause immediate splitting. The polymer solution (25 cm^3) was added to a beaker and sheared using the Silverson mixer at shear rates of <6000 rpm. To the solution, distilled water (75 cm^3) was added slowly via a syringe over a period of 10 minutes. The emulsion was then sheared for a further 20 minutes before allowing it to stand for 10 minutes. Any emulsification properties such as creaming, breaking etc were then noted. For the more stable emulsions samples was taken for DLS to measure the emulsion sphere size.

Table 6.3.3 Results of the high shear emulsion tests carried out at Nottingham University.

Polymer	M_n (GPC) (LA units)	Description	Hydrodynamic Radius (nm)
NaLPLAB004.11	~ 22	Emulsion split into two emulsion layers, O/W and W/O, Some dilatant behaviour!	715; 479 (24 h)
$MeOPEG_{750}LPLA$	~ 38	Emulsion creamed.	782
NaPLA B002.11	~19	No separation after 10 mins,	669; 559 (24 h)
NaMandelaLPLAB012	19-20	Shear thickening emulsion, v. stable, consistency of wallpaper paste.	398
Na-DL-L-PLAS003	~18	Separated quickly	267

Creaming is a term given to separation of emulsion where it appears as though cream has formed on the top. Creaming is a common phenomenon seen in the emulsions and was apparent in many of the water/squalane emulsions. It is interesting to note from the DLS data that over time the particle sizes of the emulsions decrease, this occurs as the water trapped in the particles permeates through as separation occurs. The most interesting phenomenon to be witnessed with the Water/Toluene emulsions was shear thickening behaviour.

Where shear-thinning fluids (thixotropic) are fairly common, shear-thickening (dilatant) fluids are much rarer. Dilatant or rheopectic fluids are non-Newtonian fluids whereby the viscosity increases with fluid agitation, currently there is a great interest in these types of emulsions in terms of lubricants and drilling muds, and in most cases this property is attributed to highly branched structures, where shear increases the interactions of the interactions of neighbouring particles.

The result with sodium mandelate initiated PLA may produce this phenomena, as the aromatic branch interacts much more strongly with toluene than the other PLA molecules and as such the oil phases in the emulsion particles are held much closer to the polar chain ends. This would seem to be conclusive with the DLS result where the particle sizes for this emulsion is much smaller than those recorded for the other polymers. This decrease in hydrodynamic radius, resulted in much higher emulsion stability (the emulsion had not broken after 1 month), which is due to the inability of water to permeate through the outer layers of oil and lead to the emulsion breaking. It would seem that the hydrodynamic radius relates to the dilatancy in terms of surface areas of the particles. The particles with a greater surface area per size (smaller particles) are able to interact with each other more than when

larger particles form. Increasing the rate of shear increased the amount of interaction, until an almost gelatinous paste, which the high shear mixer had great difficulty in further mixing at 6000 rpm, was formed. The shear rate had to be lowered to 1500 rpm for the duration of the test.

The photographs below illustrate the emulsification observed with water/toluene emulsions for NaMandelaLPLAB012. It is important to note that using the methods for water/squalane emulsions resulted in little to no emulsification, and that in the water/toluene emulsions high shear is required. The only system in which water/toluene emulsions have successfully been formed this way involved NaBHB initiated polymer.

After 1 day After 1 month

Figure 6.3.3 Photographs of the NaMandelaLPLAB012 emulsion after 1 day and 1 month, showing high emulsion stability.

6.3.4 Conclusion

From the above sections it is easy to see that there may be a significant future in the use of PLA as an emulsifier. The polymer shows good emulsion stability in water/squalane (1 : 1) emulsions at as well as thixotropy. It would be desirable for a much more detailed investigation of water/toluene emulsions at high shear to be carried out in the future.

6.4 Thermal Properties of PLA Polymers

One of the most important characteristics of polymers is their thermal behaviour, as this has some bearing on how a polymer may be used or processed. The physical characteristics of a polymer change with temperature and there is a wide spectrum of known thermophysical changes. Plastics are often broken into several subtypes, thermosetting plastics, thermoplastics and memory plastics.

Thermosetting plastics are highly crosslinked polymers or composites that are characterised by having very high molecular weights and being insoluble in nearly all solvents. The cross-linking gives rise to the high dimensional (shape) and thermal stability, and these polymers can only be moulded at the point of creation. Thermosetting polymers are used in such applications as insulating materials, light switches, electrical sockets, etc. due to the fact they are stable up to very high temperatures.

The most common polymers for everyday applications are thermoplastics. The main characteristics of thermoplastics are flexibility and (re-)processability. They can be melted and are usually soluble in some organic solvents. Due to this, thermoplastics are easily processed (extrusion, blow moulding, spinning etc.) and recycled. As the polymer chains in thermoplastics are not overly cross-linked, often containing only plasticizer to increase physical, thermal and mechanical strength, they have lower molecular weights than thermosetting plastics, and when heated undergo changes of state. These changes of state are characterised by the *crystallisation temperature* (T_c), *glass transition temperature* (T_g) and *melting point* (T_m) and are thermodynamically distinct. They can be measured using calorimetry (see Chapter 2.3.1).

Memory plastics are thermoplastics that, if misshapen or crushed, will return to their original shape when heated.

6.4.1 Differential Scanning Calorimetry for Thermal Analysis of PLA Polymers.

As well as assessing the aqueous and emulsification properties of these polymers, it was worth looking at the thermal properties also. As the polymers contain living chain ends there is the likelihood that when heated they will continue to react with themselves, by chain transfer, transesterification etc. The thermal properties also give an indication of the

stereochemistry of the chains as D,L-PLA polymers should have lower glass transition temperatures than L-PLA polymers, however, the differences may not be wholly significant due to relatively short chain lengths of the polymers synthesised during this study.

Procedure:

For each experiment 2-5 mg of the polymer were used. Before each set of runs (once per week) a calibration run was carried out using two empty pans. The standard for comparison was an empty pan, as the DSC compares the thermodynamic properties relative to a standard. Each experiment consisted of 3 runs from –30 ^{o}C to 150 ^{o}C and 2 reverse runs from 150 ^{o}C to –30 ^{o}C, a 5 minute isotherm was held after each run. The heating/cooling rate was 5 K min^{-1} and gaseous nitrogen was used as the coolant. Once the final run to 150 ^{o}C had been measured, the sample was allowed to cool to ambient temperature.

Results:

Table 6.4.1 The differential scanning calorimetry data for PLA based surfactants showing, glass transition temperature and heat capacity of the materials.

Name	M_n (LA units)	Onset (^oC)	Midpoint T_g (^oC)	Inflection (^oC)	End (^oC)	ΔCp^* (J (g K)$^{-1}$)
ChoPLAB007	10	14.4	20	20.1	25.7	0.493
NaPLAB002	24	11.6	18.8	19.9	26	0.695
NaPLAB002.11	26	38.5	43.4	43.4	48.4	0.486
NaPLAB002.2	13	30.1	35.3	35.4	40.5	0.587
NaLPLAB004.1	25	37.4	42.7	42.9	48.0	0.540
NaLPLAB004.11	27	41.0	44.9	44.7	48.8	0.244
NaLPLAB004.2	13	20.6	26.1	25.9	31.5	0.562
NaBHBLPLA001	6 per arm	27.6	32.9	32.9	38.3	0.555
GButLPLA001	14	27.3	32.2	31.9	37.1	0.472
NaHBuAPLA002	21	22.9	27.5	26.9	32.0	0.444
NaHBuALPLA002	25	26.6	31.8	31.7	37.0	0.522
NaHBuALPLA001	18	37.8	42.3	42.2	46.9	0.509
KHHxAPLA002	16	26.8	30.7	29.9	34.6	0.332
NaHHxALPLA002	24	33.1	38.2	38.2	43.3	0.529
NaMandelaPLA001	16	39.1	44.1	44.1	49.0	0.451
NaMandelaLPLA001	13	43.4	48.6	48.7	53.8	0.536
NaMandelaLPLA002	17	34.4	39.8	39.7	45.1	0.514
NaHHxALPLA001	7	25.6	31.1	31.3	36.6	0.592
NaHiVALPLA001	17	22.7	28.4	28.8	34.2	0.563
NaHiVALPLA002	13	24.1	29.4	29.4	34.7	0.520
NaHiVAPLA003	14	28.6	33.8	33.9	39.0	0.545
KHiVAPLA001	15	22.5	27.4	27.1	32.2	0.434
NaHiVAPLA004	28	28.8	34.3	34.6	39.8	0.575
NaLHiVALPLA002	18	32.6	38.0	38.4	43.5	0.557
NaBHBPLA002	5 per arm	23.1	28.6	28.7	34.0	0.562
NaBHBPLA003	8 per arm	36.7	40.6	39.4	44.5	0.247
NaBHBLPLA002	6 per arm	17.6	22.7	22.7	27.8	0.499
Stereoblocks						
Na-D,L-PLA001	24-25	31.9	36.8	36.4	41.6	0.489
NaLHiVA-L,D-PLA001	26	35.6	40.6	40.7	45.6	0.448
Na-D,L-PLAS003	24	29.5	34.4	34.4	39.3	0.478
Na-L-D,L-L-PLAS005	24	15.7	22	22.6	28.2	0.575
Stereoblends						
Na-D+L-PLAM002	27	26.3	32.1	32.4	37.8	0.339
Na-L,D + D,L-PLAM003	-	6.6	12.7	13.1	18.7	0.428
Na-L+D-PLAM006	19	8.4	14.7	15.1	20.9	0.515

The data in the table record all aspects of the glass transition slope, the actual glass transition temperature is taken at the midpoint which is usually approximately equal to the point of inflection. The heat absorbed or evolved during the phase change are also recorded.

Due to the thermal stability of the polymers they could not be heated to temperatures exceeding 150 ^oC or they decompose. Melting is not observed, suggesting these polymers are amorphous, even where enantiomerically pure lactide is used as the initiator. Physically this can be casually observed by the fact that enantiomerically pure L-PLA polymers are usually

opaque, but the short chain polymers are clear, the short PLA chains have more freedom of orientation and are less strongly bound together.

Some relationships to polymer structure can be observed in the data. As expected, longer polymer chains result higher T_g values. An increase in branch sizes also serves to increase T_g, yet it also throws up exceptions as well. These increases in T_g must be attributed to an increase in van der Waals forces between polymer chains, or the branches have an effect similar to what is observed amongst cross-linked polymers, where cross-linking leads to an increase in the thermal properties of the polymer. It would explain why for NaHiVA the T_g is lower than that for NaPLA or those with linear branches, as the nature of the HiVA branch is not conducive to polymer packing. It may even serve to wedge polymer chains apart, resulting in a more glassy polymer, where chains are more able to move across each other when heated.

However, the most surprising results are for the NaMandalate initiated polymers. In some ways these could be viewed as similar to the HiVA initiated polymers, however these show among the highest glass transition temperatures. The reason for the high T_g values for these polymers may be related to their structure. It has already been suggested (see Section 5.3.3) that more than one mandelate group may be present per chain, leading to higher order within the structure and giving misleading results from end group analysis – suggesting that the polymer may be longer than the NMR spectroscopic data indicates.

It is worthwhile to note the depression of T_g for the polymer blends and the stereoblocks. This shows the effect blending and stereoregularity have on the packing efficiency of polymers, which is important in relation to T_g.

The table below contains data taken for some bulk samples and shows a comparison between L and D,L PLA polymers and their T_g values. All samples are from 12 : 1 ratio PLA : initiator.

Table 6.4.2 DSC data relating M_n of D,L-PLA with L-PLA.

Initiator	D,L-PLA			L-PLA		
	M_n (LA units)	T_g (^oC)	ΔCp^* ($J(gK)^{-1}$)	M_n (LA units)	T_g (^oC)	ΔCp^* ($J(gK)^{-1}$)
XHiVA	26[a]	39.2	0.497	24-25[b]	36.8	0.534
KHHxA	22-23	35.5	0.499	26-27	38.5	0.501
NaBHB	6 per arm	39.2	0.538	11 per arm	43.9	0.496
NaMan	25	41.7	0.487	22	41.4	0.506
KHOctA	24	29.1	0.517	24	25.4	0.427

[a] X=potassium; [b] X=sodium.

The difference in glass transition temperature between D,L- and L-PLA varies only slightly in these short chain polymers. It is safer to conclude that the average chain length is more important in terms of the T_g value for these short chain polymers than the stereochemistry. It is also worth noting that a longer side chain on the initiator results in a lower glass transition, but a bulkier group leads to a higher T_g, such that the T_g for short chain PLA's follows the order of:

$$\text{Hexyl} < \text{Butyl} \leq \text{Isopropyl} < \text{Phenyl}.$$

NaBHB has been purposefully left out of this list, as it is not considered a branched initiator due to the fact it contains two arms. It is also possible there may be an ionic effect on the thermal stability, as there is a known difference in the rates of transesterification between potassium and sodium salts due to their difference in basicity.

6.5 Degradation of Polymers.

As these polymers are designed to be biodegradable it was worth investigating how they thermally degrade, it was important also to make sure the DSC data was not being compromised by polymer degradation, as some anomalies were seen during runs. Thermal gravimetric analysis (TGA) is a powerful tool to analyse the thermal stability of polymers as it details under what conditions a polymer can be processed without degrading. Being oligomers rather than true polymers the polylactides prepared in this study should have a low thermal stability, and the DSC has already shown they have low T_g values. Using TGA it was

also possible to analyse how much water was retained in the polymer aggregates as a percentage of weight, by comparing to a dry sample of the polymer.

Other than the thermal degradation of the polymers, their degradation in water and the shelf life of the polymers was also investigated. The shelf-life of the polymers and the stability in aqueous environments are important when it comes to applications of the polymers. For instance it is desirable for a detergent once used to degrade when washed away. It is not, however, desirable for the detergent to degrade prior to use, if left open to the air for a few days.

As for biodegradation (by micro-organisms) of the polymers there was no time to conduct an in depth study (as the time-frame for which can be from 0 to 18 months), however there is no reason to believe that they would not biodegrade, indeed as fairly short chain polymers they should biodegrade fairly quickly and degradation should be further facilitated by the presence of sodium or potassium ions.

6.5.1 Thermal Degradation by TGA

Procedure:

Prior to all measurements a calibration run was carried out on an empty crucible (alumina). The empty crucible was first placed on the TGA balance and set to zero. Polymer (2-4 mg) was then added and the crucible carefully replaced on the TGA balance. Once the weight had equilibrated the sample was run from 25 ^{o}C to 300 ^{o}C with a heating rate of 5 K min^{-1} in air. The heating cycle was followed by a 10 minute isothermal, before the sample was allowed to cool back to 25 ^{o}C. After each reaction the crucibles were immersed in concentrated HCl for 1 hour to remove any sticky organic deposits from the surface of the crucible. They were then washed thoroughly with water and acetone before being dried in a hot oven.

Thermal Degradation Results:

Table 6.5.1 Data on the thermal degradation of NaPLA.

Polymer	M_n	Degradation Temperature (^oC)		Overall Loss of Mass (%)
		Onset	End	
KHiVAPLAB001	26	214	259	87.9
KHHxAPLAB002	22-23	210	265	90.37
KHHxALPLAB003	26-27	190	268	61
KHiVALPLAB004	24-25	221	272	93
NaBHBPLAB006	6 per arm	207	280	86
NaBHBLPLAB007	11 per arm	215	278	89.8
NaBHBLPLA001	6 per arm	~180	~270	98
NaHiVAPLA004	28	~195	~252	92
NaHiVAPLA003	14	~148	~234	93.6
Na-D+L-PLA001	17	210	252	86.3
Na-L,D + D,L-PLAM003	-	226	270	89.1

From the table above it can be generalised that thermal degradation does not greatly alter with stereochemistry, but depends more upon the chain length of the polymers. The initiator may play a crucial role as the mobility of the cation should have an effect on the thermal degradation of the polymer. The NaBHB polymers are characterised by a long degradation range, 60-70 ^oC, although the longest degradation range was for the NaHiVAPLA which was over a range of 86 ^oC. If this is compared to longer chains where KHiVA is used it is clear that the Na salts have a greater thermal stability because the sodium alkoxide/hydroxide species are less nucleophilic than the potassium species, thus promoting less hydrolysis and transesterification

6.5.2 Water Uptake Analysis using TGA.

As well as investigating the thermal decomposition it was worth examining whether the thermal decomposition altered in the case where the polymer was wetted. As well as showing the thermal stability of the wetted polymer, TGA could also be employed to analyse how much water was retained in the polymer structure after *drying*.

This is an important premise to the project, as the project was started on the assumption that polyesters like poly(lactic acid) could be used in surfactants in the same way as polyethers like polyethylene glycol. Of course this assumption proved to be flawed as poly(lactic acid) packs far too efficiently to undergo the same level of hydrogen bonding allowed by ethers, but it still undergoes some. Whether on the surface of the polymer aggregates or by reforming the polymer chains into micelles, water does interact with PLA even when it is being used as the hydrophobe. Using TGA it is possible to quantify the ability of these polymers to retain water

Sample Preparation for Water Uptake Analysis:

Polymer (0.5 g) was added to water (20 cm^3) in a sample vial and immersed in a sonic bath for 20 minutes. The polymer was then removed and shaken vigorously for several 1-minute intervals over the period of 2 hours. The solution was allowed to stand overnight and, if present, the solid was first removed by filtration under vacuum, and then the solution was evaporated to recover smaller polymer particles on the rotary evaporator. Once the solution was removed the polymer was recovered by scraping the sides of the flask and the polymer filtrate and solute combined. The polymer was first left for several hours to dry in air before being placed in a vacuum desiccator for 24 hours over phosphorus pentoxide. The TGA of the *dried* polymer was then recorded and compared with a dry polymer sample. Any deviation in the weight loss pattern could be attributed to water loss (80 – 130 ^oC).

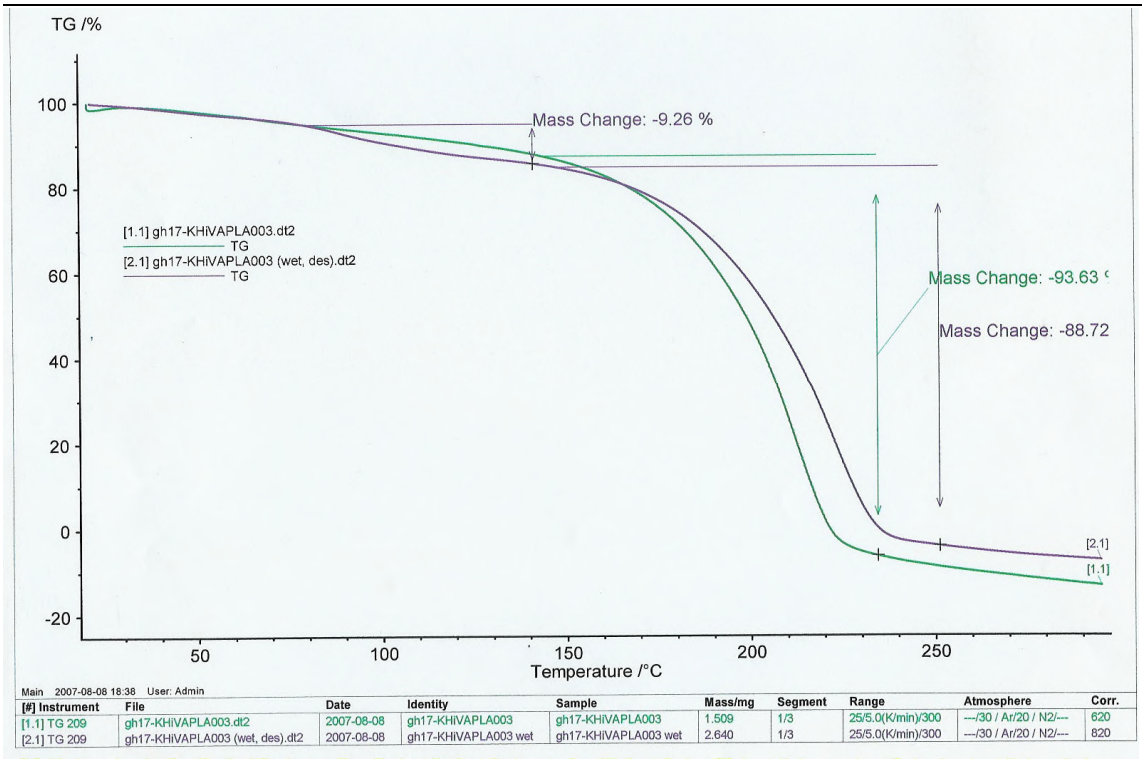
Water Uptake Results:

Table 6.5.2 Data showing the mass of water lost and overall loss in mass of NaPLA polymers before/after wetting.

Polymer	Degradation Temperature (°C)						Loss in Mass of Wetted Polymer (%)		
	Dry Polymer		Wetted Polymer						
			Water		Polymer		Water	Polymer	Overall
	Onset	End	Onset	End	Onset	End			
KHiVAPLAB001	214	259	49.9	135	214	240.9	34	62.4	96.4
KHHxAPLAB002	210	265	90.7	108.6	231.3	254.2	21.5	70.39	91.9
KHiVALPLAB004	221	272	91.7	151.6	237.8	-	16.15	95.39	100
NaBHBPLAB006	207	280	-	-	256	-	0	69.7	69.7*
NaBHBLPLAB007	215	278	-	-	229.1	259.5	0	93.6	93.6
Na-D+L-PLA001	210	252	-	-	244.2	271.5	0	94.8	94.8
NaD,L+L,DPLAM003	226	270	54.6	79	>300	>300	12.8	29.4	42.2
NaHiVAPLA004	~195	~252	~60	~130	~196	~200	17.2	87	100
NaHiVAPLA003	~148	~234	~110	~150	~170	~250	9.3	88.7	98
NaBHBLPLA001	~180	~270	-	-	~230	>300	0	~100	~100

* End point of degradation ran outside of the temperature range, so measurements were recorded up to 300 °C.

From the water uptake analysis several interesting things were noted. In the case of the branched initiators the polymers were able to retain between 9 and 34 % by mass of water. This is a significant amount of water retained in these polymers. What is even more interesting to note is that wetting the polymers in some cases led to an increase in polymer degradation temperature as well as often increasing the overall loss in mass - as would be expected. This increase in degradation temperature suggests that the formation of polymer micelles has a stabilising effect on the thermal stability. It had been assumed that wetting the polymer would result in a lower thermal stability due to the presence of water leading to rapid hydrolysis. What is in fact the case is that both of these effects are happening; the micellar arrangement increases the thermal stability i.e. the temperature at which degradation begins; however, the temperature range over which this degradation occurs is often reduced as a result of hydrolysis. The TGA shown in Figure 6.5.2a illustrates this point.



[#] Instrument	File	Date	Identity	Sample	Mass/mg	Segment	Range	Atmosphere	Corr.
[1.1] TG 209	gh17-KHiVAPLA003.dt2	2007-08-08	gh17-KHiVAPLA003	gh17-KHiVAPLA003	1.509	1/3	25/5.0(K/min)/300	---/30 / Ar/20 / N2/---	620
[2.1] TG 209	gh17-KHiVAPLA003 (wet, des).dt2	2007-08-08	gh17-KHiVAPLA003 wet	gh17-KHiVAPLA003 wet	2.640	1/3	25/5.0(K/min)/300	---/30 / Ar/20 / N2/---	820

Figure 6.5.2a TGA curves for wetted (navy blue) and dry (turquoise) NaHiVAPLA003 polymer.

Another interesting set of results were those from the NaBHB initiated polymers. In these cases the amount of water uptake was zero. However, the thermal and degradation stability of the polymers was increased (figure 6.5.2b.). In this case and for the other BHB polymers the thermal stability was increased considerably, with a temperature range increase of between 15 and 50 ^{o}C. This goes some way to support our previous proposal that BHB initiated polymers, more than any other, have the ability to rearrange their shape in aqueous or organic media to maximise interactions and stability. It was surprising that these polymers did not show greater water retention than the other PLA polymers. Interestingly the polymer blend also showed the same type of behaviour as the BHB initiated polymers (Figure 6.5.2c), but this cannot be explained in the same way. It may be that the increase in thermal stability results from different micellar packing phenomena due to the way PLA chains of different stereochemistry interact. Looking at the DLS data for polymer blends, the closest example to this polymer had a very low hydrodynamic radius, suggesting that the polymer interactions within the micelles were strongly excluding water, which would reduce swelling to a larger hydrodynamic radius.

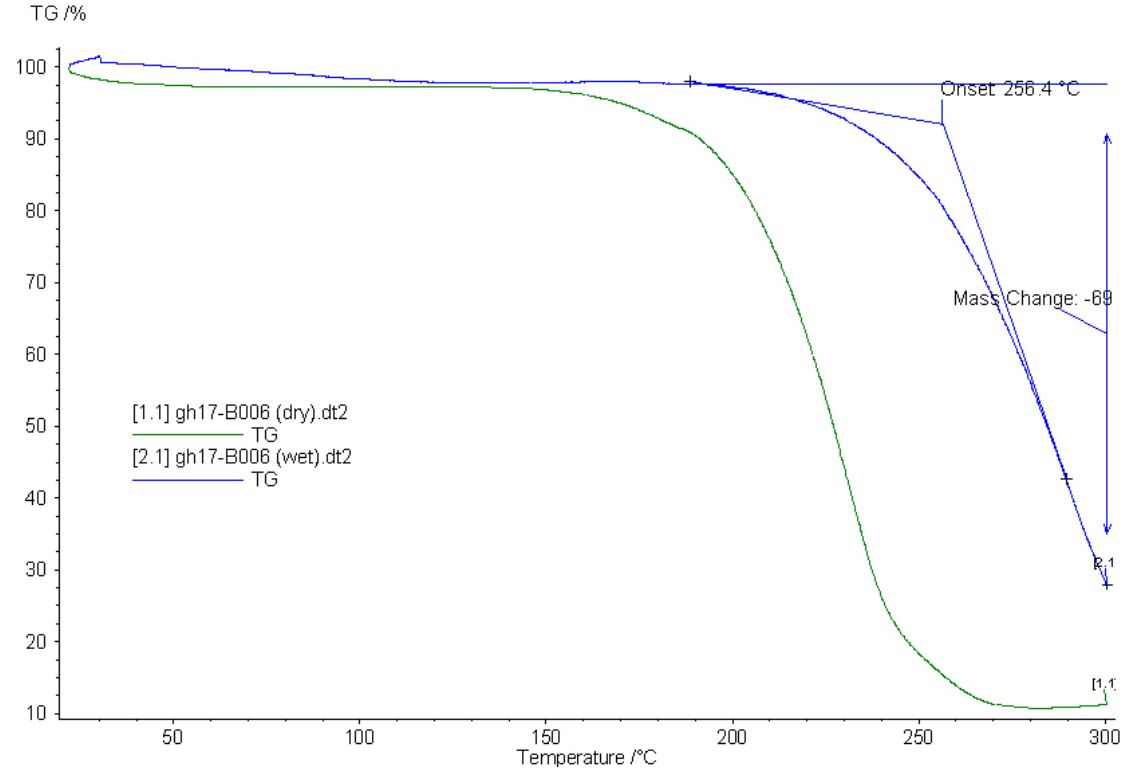


Figure 6.5.2b TGA showing the degradation for NaBHBPLAB006.

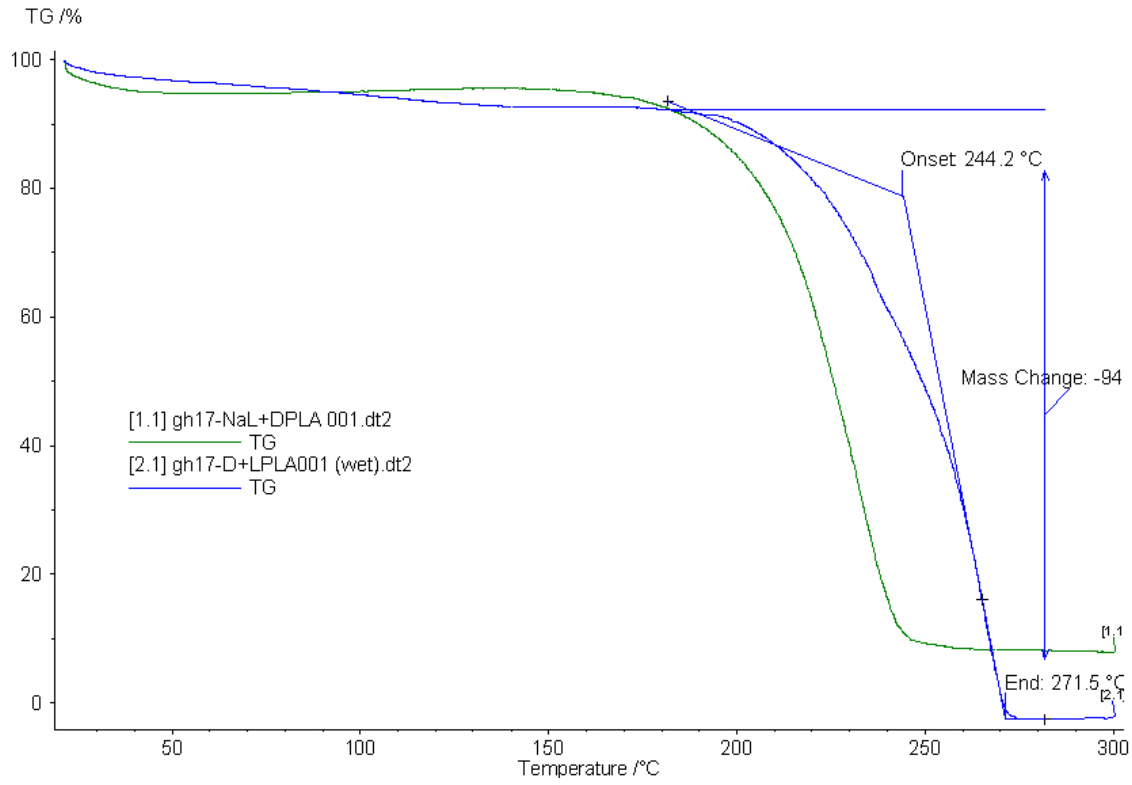


Figure 6.5.2c TGA analysis of Na-D+L-PLA001.

6.5.3 Polymer Decomposition in Water.

Polymer decomposition has been observed for many of the sodium and potassium PLA polymers when left in water for an extended period (> 2 months). The polymer degradation occurs faster where the polymer concentration is low 1-2 mg cm^{-3}. Where high aggregation or polymer emulsions are formed this degradation is not observed even at 4-6 months and 1 year respectively. With polymer degradation, the surfactant ability etc is lost.

The major characteristic of the decomposition in water is the formation of a brown/black mould with a web-like appearance. Attempts at characterising this mould using NMR techniques etc were unsuccessful due to two common occurrences:

1) The decomposed polymer is insoluble in nearly all common solvents therefore NMR characterisation or mass spectrometry are impossible.
2) When the mould is removed from water and dried it shrinks considerably in size, making it difficult to aquire the necessary amounts for analysis.

The photograph (Figure 6.5.3) below shows the formation of a typical mould formed from PLA when it degrades in water. In this case the mould was produced by the degradation of NaHHxAPLA001, and is not limited to the sodium salts. The choline chloride polymers are also known to degrade in water to these moulds, often faster than the sodium or potassium salts.

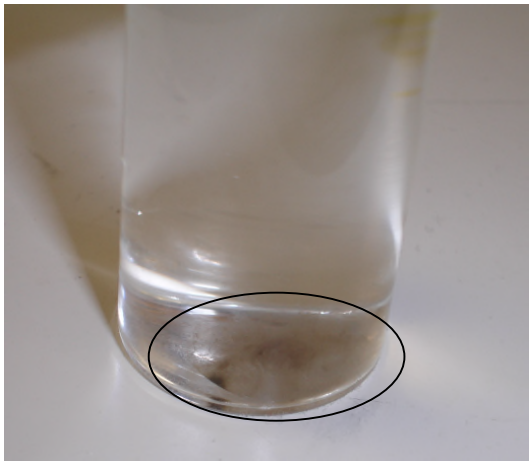


Figure 6.5.3 Mould produced after a 1 mg cm^{-3} sample (sodium mandelate : D,L-lactide; 1 : 12) was left for >4 months in water. The area circled is where the mould is located for clarity.

6.5.4 Shelf Life

Re-analysis of some of the polymer produced during June 2006 can give some indication of the expected shelf life of these polymers. If the M_n value shows a significant decrease then the polymers degrade under normal storage conditions.

Results on 3 L-PLA polymers prepared June 2006.

Polymer	L : I Ratio	M_n (2006) (LA units)	M_n (2008) (LA units)	Presence of Lactic Acid after 2 years?
NaLPLA001	6 : 1	12	6	broad peak; 4.2 ppm
NaLPLA002	12 : 1	16	9	Quartet; 4.3 ppm
NaLPLA003	20 : 1	26	14	No peaks at 4.1 to 4.2 ppm

It seems apparent that after 2 years the polymers have degraded to approximately half their original size. Given the lack of lactic acid signals in the ^{1}H NMR spectrum of NaLPLA003, this suggests the polymers degrade by breaking in the middle of chains rather than cleaving off the ends, resulting in shorter chains. A much more elaborate study could be carried out when further application tests are carried out, perhaps sampling the polymers at 1 month, 3 months, 6 months, 1 year etc., to properly ascertain the exact shelf life of these materials. As it stands these materials, if stored in air will degrade to around half their original mass in 2 years. This agrees with previous studies on PLA degradation [7] where the initial step is internal hydrolysis to lower weight chains. This degradation is facilitated by the presence of acid/base, i.e the sodium end-groups in this case producing some hydroxide in the presence of moisture from the air (Figure 6.5.4). As the polymers are not subjected to an environment where bacteria and/or other microorganisms can cause degradation, no loss of mass to CO_2, water and humus should be occurring.

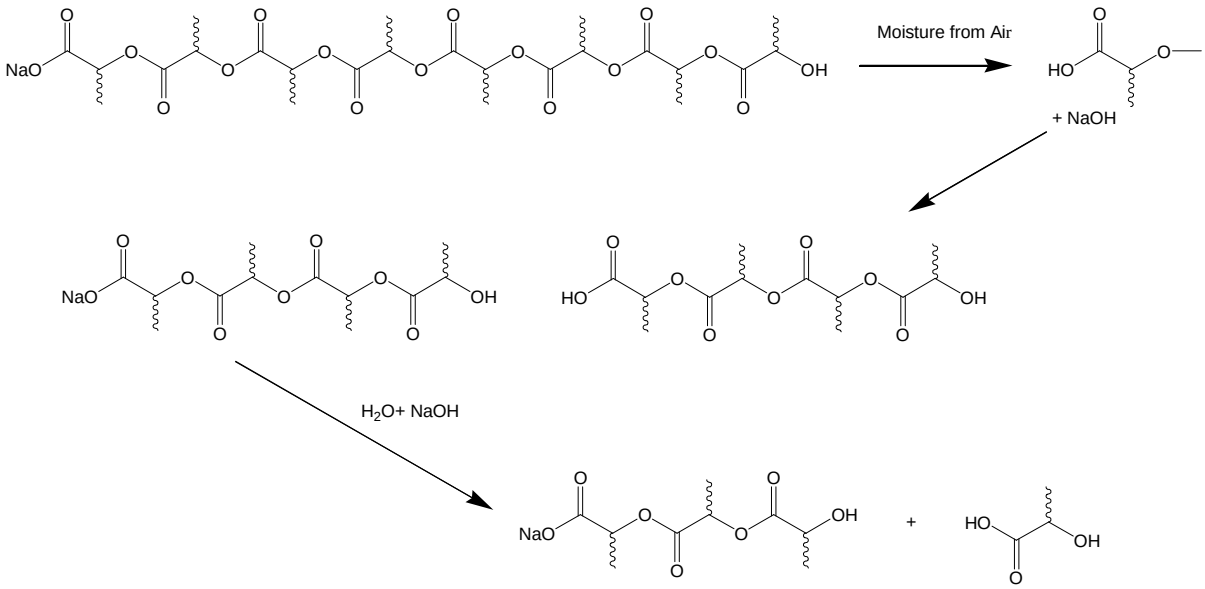


Figure 6.5.4 Illustration of the hydrolysis degradation occurring in NaPLA polymers.

6.5.5 Conclusion

Using TGA and time it was possible to look at the stability of NaPLA polymers and their micelles. The results are promising in terms of using the polymers as biodegradable surfactants and emulsifier materials, but the thermal stability of the polymers is quite low making them unsuitable for purposes that require using the polymer in the molten state, such as moulding etc. The results on the degradation of the polymer in air, showing a reduction in chain length by half after 2 years, suggest that any application of these polymers should be carried out within 6 months to a year of preparation of the polymer, or the polymer should be stored for longer periods under an inert atmosphere.

6.6 Conclusion

From the results in this chapter it is clear that short chain NaPLA polymers show some characteristic differences from long chain PLA reported by other authors and the other PLA polymers prepared in chapter 3 and 4 of this work. A further study into the emulsion properties of these polymers would be interesting as would a microscopy study of the resulting micelles and aggregates to confirm vesicle formation and to establish if aggregates are formed by the coalescence of micelles or by coalescence of insoluble polymer material.

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Conclusion & Further Work

The main brief of this project was to investigate Poly(lactic acid) as a biodegradable hydrophile, using the more environmentally benign and more efficient ROP of lactide rather than polycondensation or chain extension of lactic acid.

Hydrophilicity of PLA.

It was initially hypothesised in the Uniqema proposal that polyesters, could, under the right circumstances produce hydrophilic behaviour similar to polyethylene glycol, with perhaps showing a higher availability of H-bond acceptors in the form of C=O groups. From the study it can be concluded that due to high electrostatic interactions between polymer chains, especially where the chains have a high degree of order, this behaviour cannot occur. Therefore poly(lactic acid) is a poor hydrophilic polyester, but other polyesters, may exist that exhibit better hydrophilic behaviour. In order to improve the hydrophilicity of these polyester systems there are several approaches that could work in the future:

1) Reduce the amount of order in the polyester chains as *rac*-PLA was hydrophilically better than L-PLA. Incorporation of random glycolic acid units may improve water solubility.
2) Reduce the linearity of the polymer chains with branching either by use of glycerol (glycerol carbonate) [1] unit or 2,2-bishydroxymethylbutyric acid units incorporated into the structure to give branching. However deviations form linearity will result in different polymer and surfactant behaviour.
3) Try capping the end of the PLA with a more polar group such as an ammonium group or trimethylammonium, a sulfonated group or by addition of a cation.

Hydrophobic PLA.

After the initial disappointment that PLA was more hydrophobic than initially suggested, it seemed logical to investigate these properties of PLA. This was interesting as it opened the way for some research into new initiators for ROP of PLA and the move away from toxic transition or heavy metal catalysts and DMAP.

It was discovered that choline chloride can be used to ROP lactide in the presence of urea, a reaction that was so far un-investigated. This had several interesting associations, the first was that choline chloride has a very high mpt. 305 ^{o}C, but in the presence of urea (ratio 1 : 1 to 3 : 1) at 100 ^{o}C it forms an eutectic mixture. This eutectic mixture in the melt with lactide is sufficient to ROP and form fairly predictable polymers in terms of M_n. These choline chloride initiated polymers show very good surfactant ability, but are not very promising as emulsifiers.

Another interesting discovery followed on from the work by Kricheldorf *et al.* [2], who had looked at the sodium and potassium salts of lactate and mandelate as PLA initiators. Their conclusion was that they are poor initiators and cannot be used to produce high mwt. PLA. This was interesting in the scope of our project because, although we cannot produce very long chains, it would offer a method of producing PLA surfactants in a one step process.

It has been shown the PLA can be produced in this one step process and the system can be initiated by an assortment of sodium/potassium salts of β and γ hydroxyacids. These polymers show surfactant ability as well as some emulsification properties.

Following on from this work it is possible in future to develop these systems further, a brief encounter with sodium valinate showed that this also works effectively as a ROP initiator for lactide with incorporation of valine, this also showed reasonable surfactant ability. It is therefore feasible that many other amino acids could be developed to produce the same sort of results. If longer polymer chains are attainable through this method it could open new methods for the production of biocompatible PLA's for biomedical and personal care applications, where there are no toxic metal catalysts and no volatile organic solvents involved and all the biodegradable components can be safely metabolised and excreted from the body.

It would also be worth continuing the studies on poly(lactic acid) stereoblends [3], stereoblocks [4] and a deeper look at forming poly(lactic acid) cycles, that there was some evidence suggesting it could be a mechanism present in some of the reactions.

Applications Testing.

The polymers produced by ROP of lactide by sodium/potassium hydroxyacids all showed some surfactant properties. The polymers had very low CMC showing a high degree of rearrangement in water. Polymer chains of around 10 – 18 LA units showed good surfactant ability and were slower to aggregate, polymers of 20 LA units and greater showed better emulsification ability but were hampered by poorer solubility in water. In water/squalane emulsions under mild shearing conditions (shaking) some of these polymers produced thixotropic (shear thinning) emulsions. Once the emulsion was formed and allowed to rest it thickened to the point where it was almost gelatinous. When shaken the viscosity of the emulsion was reduced. Water/toluene emulsions showed different characteristics largely due to the fact that toluene was the phase containing the emulsifier.

Some water uptake studies were also carried out on the polymers using TGA. These showed two interesting scenarios, one where water was held by the polymer and another where water may/may not be incorporated but the thermal stability of the polymer increases due to rearrangement of the polymer molecules in solution. A much deeper study of this behaviour should be carried out, perhaps incorporating TGA-MS to conclusively show water being given off at point X on the thermogram etc.

There is much further work required in this area in terms of analysis of the polymers and applications testing. Due to time constraints some experiments that were planned on emulsification using an Ultraturax have as yet to be carried out. Detailed testing of the emulsion rheology would also be worthwhile investigating to prove true shear thinning behaviour etc, and a proper biodegradation study incorporating all of these systems would also be beneficial.

Another method worth investigating in future studies would be looking at different foaming methods and how these lead to or reduce aggregation. It might be worth investigating by bubbling gas/compressed air through the system to see how much foam/bubbles are produced and whether if the polymer aggregates, do these aggregates contain pockets of gas/air causing them to float. It may also be worth looking at polymer aggregates and sediment using electron microscopy to look at trends in shape, size etc.

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